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Decellularized Matrices for the Treatment of Tissue Defects: from Matrix Origin to Immunological Mechanisms

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Abstract

Decellularized matrix transplantation has emerged as a promising therapeutic approach for repairing tissue defects, with numerous studies assessing its safety and efficacy in both animal models and clinical settings. The host immune response elicited by decellularized matrix grafts of natural biological origin plays a crucial role in determining the success of tissue repair, influenced by matrix heterogeneity and the inflammatory microenvironment of the wound. However, the specific immunologic mechanisms underlying the interaction between decellularized matrix grafts and the host immune system remain elusive. This article reviews the sources of decellularized matrices, available decellularization techniques, and residual immunogenic components. It focuses on the host immune response following decellularized matrix transplantation, with emphasis on the key mechanisms of Toll-like receptor, T-cell receptor, and TGF-β/SMAD signaling in the stages of post-transplantation immunorecognition, immunomodulation, and tissue repair, respectively. Furthermore, it highlights the innovative roles of TLR10 and miR-29a-3p in improving transplantation outcomes. An in-depth understanding of the molecular mechanisms underlying the host immune response after decellularized matrix transplantation provides new directions for the repair of tissue defects.

Key Words: Decellularized matrices, Allogeneic or xenograft, Host immune response, Signal transduction, Macrophages, T cells

INTRODUCTION

Acute injuries, such as trauma, high-voltage electric shock, strong acid burns, and strong alkali burns, as well as chronic injuries, including pressure injuries, radiation injuries, and diabetic foot injuries, often result in tissue defects (Byun *et al*., 2019; Guan *et al*., 2021; DePamphilis *et al*., 2022; Di *et al*., 2022; Lacroix *et al*., 2023; Kedar *et al*., 2024). The clinical management of defective tissues is challenging and prolonged, prone to infections, sepsis, and other complications, posing a serious threat to patients' lives and well-being. While conventional clinical dressings can temporarily cover defective wounds, they cannot serve as long-term grafts to support tissue remodeling and growth (Chang, 2023). Consequently, repairing tissue defects remains a formidable clinical challenge.

Decellularized matrices, derived from the tissues of allogeneic or xenogeneic organisms, have emerged as a potential solution. Through decellularization, immunogenic components such as cells, deoxyribonucleic acid (DNA), α-galactosidase (α-Gal) epitopes, and major histocompatibility complexes (MHC) can be removed, preserving the three-dimensional structure and fibrous components of the extracellular matrix (ECM) of natural tissues (Duisit *et al*., 2018; Liu *et al*., 2022; Wei *et al*., 2023). The ECM serves as a micro-environment for tissue-resident cell adhesion and communication. Compared

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to conventional clinical dressings, decellularized matrices possess unique bioactivities and hold promise for promoting the repair of defective tissues as long-term grafts. The host immune response triggered by decellularized matrix grafts is a topic of intense debate among researchers (Talaei-Khozani and Yaghoubi, 2022; Hou *et al*., 2023; Liang *et al*., 2023).

Following decellularized matrix transplantation, the host immune system recognizes the graft as a non-self component, activating immune cells such as neutrophils, macrophages, and T cells. These activated immune cells secrete or express immune molecules, including immunoglobulin (Ig), complement system components, and cluster of differentiation (CD) markers, which exert immune recognition and regulation through Toll-like receptors, scavenger receptors, and T-cell receptors (de Almeida Coelho *et al*., 2019; Shao *et al*., 2019; De Trez *et al*., 2020; Shepherd and McLaren, 2020; Wei *et al*., 2021; Hildebrandt *et al*., 2023). Studies have demonstrated that TGF-β, microRNA (miRNA), and other substances can exert immunomodulatory effects. An effective immune response enables the body to maintain internal environmental stability. Conversely, a foreign body reaction characterized by a fibrotic envelope can lead to receptor infection, thrombosis, and tissue damage (Liang *et al*., 2023).

Numerous studies have employed immunological and histological approaches to demonstrate the safety and efficacy of decellularized matrix transplantation using tissue-deficient animal models and clinical trials. However, the molecular mechanisms underlying decellularized matrix-mediated host immune responses have been less frequently reported (Jiang *et al*., 2019; Wang *et al*., 2021; Xia *et al*., 2023). Insights into these mechanisms of decellularized matrix-mediated immunology have contributed to the development of effective transplantation strategies to prevent foreign body reactions.

DECELLULARIZED MATRIX

Decellularized matrices derived from natural biological sources have the potential to support the long-term growth of host tissues. Although a wide array of decellularization methods are available, residual immunogenic components inevitably trigger host immune responses. Therefore, it is essential to explore the three key perspectives of matrix origin, decellularization techniques, and immunogenic components.

Sources of decellularized matrix

Autologous or allogeneic biological sources: For human recipients, autologous or allogeneic biologically-derived decellularized matrices are typically taken from clinical procedures or human donors. There is currently strong clinical evidence for the use of human-derived decellularized matrices (Melandri *et al*., 2020; Salinas Ramila *et al*., 2021; Salinas *et al*., 2022). However, there are issues of ethics, high cost, and restricted sources (Saricilar and Huang, 2021).

Autologous tissue transplantation has gained significant momentum, with autologous skin grafts being the most prevalent, with the advantage of virtually no immunogenic complications and the ease of tissue viability after transplantation, thus eliminating the need for decellularization for autologous tissue transplantation (Tardalkar *et al*., 2022). However, autologous grafts are associated with high donor site damage and limited sources, making a decellularized matrix of allogeneic biological origin a potential alternative. Recent studies have indicated that decellularized allogeneic dermis (Beijing Jieya Laifu Biotechnology Co., Ltd., Beijing, China) in combination with autologous ultrathin split-thickness skin grafts can help alleviate the above-mentioned deficiencies and facilitate the treatment of burns and traumatic wounds (Chen *et al*., 2024). The decellularized matrices of allogeneic biological sources are summarized below (Table 1).

Current reports for human-derived decellularized matrix (HADM) usually use commercially available products (Melandri *et al*., 2020; Fernandez-Moure *et al*., 2021). Fernandez-Moure JS *et al*. tested the efficacy of platelet-rich plasma in the repair of abdominal wall defects in male Lewis rats based on a commercially available HADM (Lifecell, Branchburg, NJ, USA) (Fernandez-Moure *et al*., 2021). Jiang *et al*. (2019) recruited 24 patients with clear limbal corneal degeneration and performed matrix endothelial corneal transplantation using HADM (Qingyuanweiye Bio-tissue Engineering, Beijing, China), and regularly evaluated the patient's ocular symptoms and signs as well as graft characteristics, demonstrating the clarity, biocompatibility, and safety of HADM in matrix endothelial corneal transplantation (Jiang *et al*., 2019). According to European legislation, HADMs are classified as "human products" rather than "medical devices" and therefore commercialization is limited (Melandri *et al*., 2020).

Xenobiotic sources: Compared with human-derived decellularized matrix, heterologous decellularized matrix, such as porcine acellular dermal matrix (PADM), goat acellular cartilage matrix (GACM), acellular fish skin matrix (AFSM), etc., are widely available at low cost (Das *et al*., 2021; Park *et al*., 2022; Melkonyan *et al*., 2023; Wei *et al*., 2023). Due to the inherent heterogeneity, the problems of immune rejection and infection caused by immunogenic components and potentially heterologous microorganisms, etc., are critical despite a range of decellularization means (Khoury *et al*., 2012; Plymale *et al*., 2020). There is evidence of minimal long-term differences between HADM and PADM after transplantation, but acute immune rejection is present in the short term in PADM (Saricilar and Huang, 2021). Therefore, more studies are needed to justify the shift from HADM to PADM.

Many studies have been conducted to provide a substantial basis for the safety and efficacy of the application of allogenic decellularized matrix grafts after transplantation (Holton *et al*., 2005; Kumar *et al*., 2014; Tellarini *et al*., 2023). Wang *et al*. (2021) obtained that compared with acellular cartilage matrix, acellular dermal matrix is a superior strategy for cartilage regeneration, as evidenced by the re-colonization and *in vitro* culture of goat auricular chondrocytes, the expression of cartilage-related genes including Aggrecan (ACAN), Collagen Type II Alpha 1 Chain (COLIIA1), and Sex-determining region of Y chromosome (SRY)-box transcription factor 9 (Sox9), and the histological and immunological evaluation of subcutaneous implantation in goats. Acellular dermal matrix (ADM) was found to be a superior strategy for cartilage regeneration compared to acellular cartilage matrix (ACM) (Wang *et al*., 2021). Xu *et al*. (2012) implanted PADM (Conexa) with the removal of α-Gal epitopes into African green monkeys and demonstrated that PADM promotes rotator cuff repair in primates by histological morphology, immunochemical methods, and serum analyses of PADM grafts after implantation. The decellularized matrices of xenobiotic origin are summarized below (Table 2).

Table 1. Application cases of decellularized matrices of allogeneic biological origin

Research area	Matrix source	Matrix application	Effectiveness	References
Clinical	J-1 decellularized allogeneic dermis (Beijing Jieya Laifu Biotechnology Co., Ltd., Beijing, China)	Treatment of clinical burns and trauma wounds	No rejection found	Chen *et al*., 2024
Clinical	HADM (The Skin Bank of the Bufalini Hospital, Cesena, Italy)	Treatment of clinically exposed wounds of the distal tendon of the lower extremity	At 7 days postoperatively, 95% of the grafts were absorbed with no signs of hematoma	Melandri *et al*., 2020
Clinical	HADM (Qingyuanweiye Bio-tissue Engineering Co., Ltd., Beijing, China)	Clinical stromal endothelial corneal transplantation	Grafts healed at 6 months postoperatively and re-epithelialization was completed	Jiang *et al*., 2019
Clinical	Decellularized dermal matrix graftjacke® (Wright Medical Technology, Arlington, TN, USA)	Treatment of failed clinical first metatarsophalangeal joint implant replacements	Integration of graft material into the joint with satisfactory function	Khoury *et al*., 2012
Animal	HADM with or without the addition of platelet-rich plasma (Alloderm®; Lifecell, Branchburg, NJ, USA)	Ventral hernia repair in male Lewis rats	Addition of Platelet-Rich Plasma Alloderm Reduces Early Inflammatory Response	Fernandez-Moure *et al*., 2021
Animal	HADM	Improved long-term projection of the nipple flap in thymus-free rats	HADM is able to maintain long-term projection	Holton *et al*., 2005

HADM, human acellular dermal matrix.

Table 2. Examples of applications of decellularized matrices of xenobiotic origin

Research area	Matrix source	Matrix application	Effectiveness	References
Animal	PADM	Treatment of hernia defects in pigs	Grafts replaced by newly formed connective tissue	Melkonyan *et al*., 2023
Animal	AFSM	Treatment of deep second-degree burn wounds in male KM mice	No adverse acute pro-inflammatory reactions	Wei *et al*., 2023
Animal	GACM	Reconstruction of cartilage defects in rabbits	No significant immune response or tissue rejection	Das *et al*., 2021
Animal	PACM, PADM (JiangSu Unitrump Biomedical Technology Co., Ltd., Jiangsu, China)	Subcutaneous implantation in the abdominal rib area of goats	Lower PADM-induced immune response	Wang *et al*., 2021
Animal	Cell-free rabbit dermal matrix	Treatment of lateral ventral hernia in buffaloes	Post-operative rehabilitation	Kumar *et al*., 2014
Animal	PADM (Conexa Reconstructive Tissue Matrix; Tornier Inc, Edina, MN, USA)	Repair of supraspinatus tendon defects of the rotator cuff in the African green monkey	No Hypersensitivity Reaction	Xu *et al*., 2012

PADM, porcine acellular dermal matrix; AFSM, acellular fish skin matrix; GACM, goat acellular cartilage matrix; PACM, porcine acellular cartilaginous matrix.

Decellularization methods

The goal of decellularization is to effectively remove cellular and nuclear components, minimizing immunogenicity while maximizing the preservation of ECM component integrity, bioactivity, and mechanical properties. Currently, various decellularization techniques, including physical, chemical, and biological enzymatic methods and their combinations, have been applied in clinical practice or animal models (Moffat *et al*., 2022). Selecting an appropriate decellularization method is fundamental to ensuring transplantation safety.

Common physical methods include repeated freezing and thawing, cycling high hydrostatic pressure, and supercritical fluids of carbon dioxide, which cause cell death by disrupting the cell membrane structure through the sustained cyclic action of critical temperature, pressure, or both (Zemmyo *et al*., 2020; Huang, 2021; Yang *et al*., 2022). Chemical methods mainly include the use of acids, bases, ionic detergents (e.g., sodium dodecyl sulfate (SDS), sodium deoxycholate, Triton X-200), non-ionic detergents (e.g., Triton X-100), and amphoteric detergents, etc., which can change the permeability of cell membranes and ultimately cause the cells to swell and rupture to achieve the purpose of decellularization. SDS treatment is considered a powerful decellularization method, but the induced matrix damage appears to be irreversible (Shin *et al*., 2019; Yamanaka *et al*., 2020; Isidan *et al*., 2021; Meşina *et al*., 2023). Bioenzymatic methods typically utilize trypsin, phospholipase A, DNAase, and ribonucleic acid (RNA) enzymes to selectively degrade proteins in the cell matrix or to hydrolyze deoxyribonucleotide chains and terminal nucleotides in nucleotide chains (Fig. 1) (Wu *et al*., 2009; Nayakawde *et al*., 2020; Xia *et al*., 2023).

However, different decellularization methods all lead to varying degrees of disruption of the ultrastructure of the decellularized matrix, deterioration of mechanical properties, and uncontrolled degradation (Da *et al*., 2021). The above methods are often used in combination to develop and refine effective decellularization strategies. Xia *et al*. (2023) prepared a novel PADM using a combined decellularization method of trypsin, neutral protease, and SDS solution and tested for graft activity, immunogenicity, and degree of vascularization, demonstrating that the PADM was effective and safe for transplantation in Sprague Dawley (SD) rats (Xia *et al*., 2023). Alaby Pinheiro Faccioli *et al*. (2022) showed that the decellularization of porcine liver (~1.5 kg) for 3 days using a combination of chemical and enzymatic decellularizers (trypsin, sodium deoxycholate, and Triton X-100) was effective in achieving cellular removal, retention of the ECM component, and vascular bundle integrity (Alaby Pinheiro Faccioli *et al*., 2022).

In general, tissues were considered decellularized by (i) possessing double-stranded DNA content less than 50 ng/mg of dry weight tissue content, (ii) DNA fragments of only less than 200 base pairs, and (iii) the absence of visible nuclear material in the 4,6-diamidine-2-phenyl indole (DAPI) and hematoxylin-eosin (HE) staining without visible nuclear material (de Paula *et al*., 2023). However, it is worth exploring whether this criterion correctly assesses the true immunogenic component residue. Bruyneel and Carr (2017) demonstrated that standardization of decellularization to dry or wet weight may be misleading and proposed an alternative strategy: standardization to units of whole organ or whole initial organ weight. Correctly assessing decellularized tissue composition is important for exploring effective decellularization strategies and clinical conversion (Bruyneel and Carr, 2017).

Immunogenic components in the decellularized matrix

Heterologous antigens represented by α-Gal epitopes and MHC molecules are a major obstacle to the use of decellularized matrix in clinical practice (Wong *et al*., 2013). The α-Gal

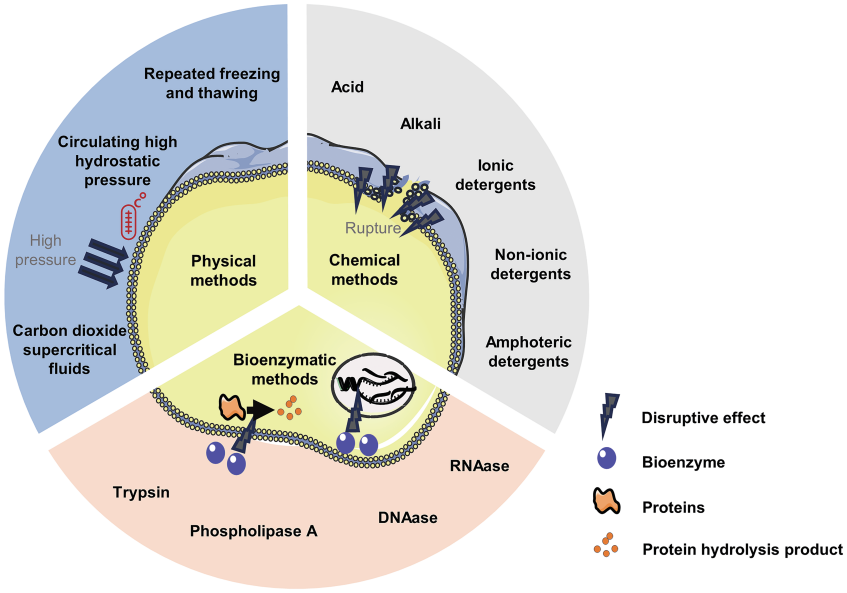

Fig. 1. Common decellularization methods and their examples. Physical methods cause cell death by disrupting the cell membrane structure through the continuous cyclic action of critical temperature, pressure, or both. Chemical methods alter cell membrane permeability, ultimately leading to cell expansion and rupture for decellularization. Bio-enzymatic methods typically selectively degrade proteins in the cell matrix or hydrolyze deoxyribonucleotide chains and terminal nucleotides in the nucleotide chains.

epitope is prevalent in non-primate mammals, marsupials, and New World monkeys, but not in humans, apes, or Old World monkeys. Anti-Gal antibodies are naturally present in the human body. Residual alpha-Gal epitopes in the decellularized matrix bind specifically to anti-Gal antibodies, leading to hyperacute and acute immune rejection induced by xenotransplantation (Huai *et al*., 2016; Morris *et al*., 2017). MHC is present in almost all vertebrates, and polymorphisms of the MHC gene are evident in different species and individuals. MHC molecules on donor cells can be recognized by T cells, mediating the immune rejection triggered by allogeneic transplantation (Radwan *et al*., 2020; Halm *et al*., 2021; Carnel *et al*., 2023).

In addition to α-Gal epitopes and MHC molecules, immunogenic components on decellularized matrix include cellular components including nuclear DNA, mitochondrial DNA, microtubule proteins, and ECM proteins such as collagen, elastin, laminin, fibronectin, and proteoglycan (Bilodeau *et al*., 2020). A recent study using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to examine the proteomic profiles of 12 commercially available decellularized matrices showed that almost all of the decellularized matrix retained essential structural proteins, and half of the decellularized matrix also retained functional proteins, with the number of identified proteins ranging from 7 to 106 (Wang and Sun, 2023). Structural proteins contribute to the extracellular protein-protein interaction network that supports cell behavior and tissue regeneration. However, Type I collagen, type V collagen, and k-alpha 1 microtubule proteins have been identified as immunogenic lung-restricted antigens, which may play a predominant role in the rejection of allogeneic lung transplants (Akbarpour *et al*., 2019).

In addition, reagents used in the decellularization process, standardization of decellularization, the applicability of animal studies to humans, source of the decellularized matrix, timing of the immune response, and possible bacterial and viral infections are all potential threats that affect the immune response after transplantation (Bilodeau *et al*., 2020).

In response to post-transplantation adverse reactions caused by immunogenic components, knockout animals have gained significant momentum, such as the α-Gal knockout (α-Gal-KO) mouse and the α-1,3-galactosyltransferase knockout (GalT-KO) minipig (Gock *et al*., 2000; Barone *et al*., 2015; Platz *et al*., 2016). In addition, protein inhibitors of activated signal transducer and activator of transcription 1 (STAT1; PIAS1), a negative regulator of cytokine signaling and potent immunosuppressive proteins, can be used as a predictive marker of graft outcome, although its molecular mechanism is unclear and has not been studied in decellularized matrix transplantation (Nafar *et al*., 2020).

HOST IMMUNE RESPONSE INDUCED BY DECELLULARIZED MATRIX TRANSPLANTATION

Following implantation of the decellularized matrix into the recipient, the triggered host immune response can be divided into the following phases in chronological order: selective adsorption of plasma proteins to the surface of the decellularized matrix, recruitment and interaction of immune cell populations in a dynamic inflammatory micro-environment, and either successful integration of the decellularized matrix with the host tissue or the occurrence of a foreign-body reaction revealing the graft outcome (Fig. 2) (Liu *et al*., 2022; Xu *et al*., 2022).

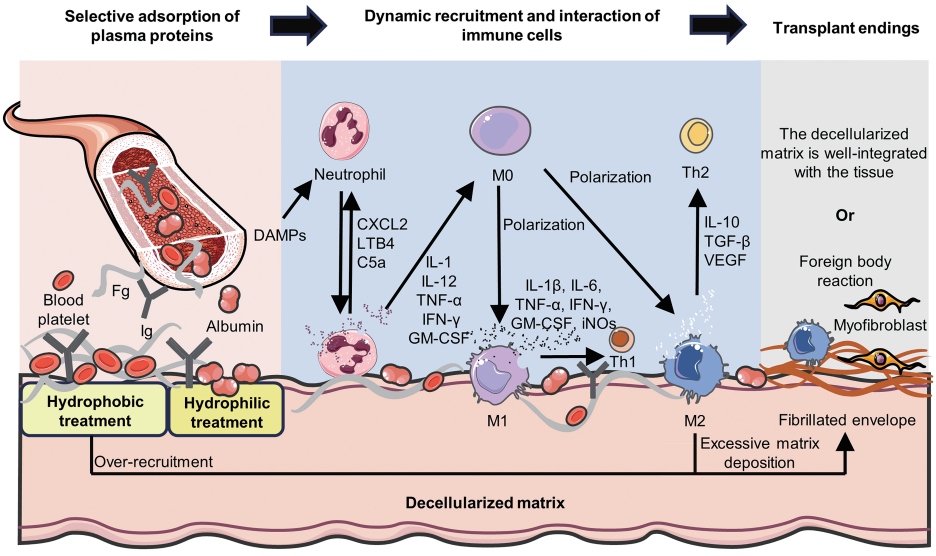

Fig. 2. Host Immune Response Induced by Decellularized Matrix Transplantation. Upon transplantation, the decellularized matrix triggers a dynamic host immune response. Initially, plasma proteins selectively adsorb to the matrix surface, with albumin preferentially binding to hydrophilic regions and fibrinogen (Fg) to hydrophobic areas. Subsequently, immune cell populations are recruited and interact within the evolving inflammatory microenvironment. In response to damage-associated molecular patterns (DAMPs), neutrophils are the first to infiltrate the transplantation site, secreting factors that polarize macrophages towards an M1 phenotype. As the inflammatory milieu progresses, macrophages transition to an M2 phenotype, eliciting a Th2 immune response. Ultimately, the decellularized matrix either integrates with the host tissue or undergoes a foreign body reaction, determining the graft outcome. Ig, immunoglobulin.

Selective adsorption of plasma proteins on the surface of the decellularized matrix

Upon implantation of the decellularized matrix into the recipient, plasma proteins adsorb to the surface of the matrix in an entropy-driven manner (Jing *et al*., 2021). Albumin, fibrinogen (Fg), and Ig are the most abundant proteins in plasma and typically dominate the surface of the implanted grafts (Daly *et al*., 2012; Love and Jones, 2013; Croes *et al*., 2019; Mishra and Pathak, 2019; Fitzgerald and Kagan, 2020). Changes in protein conformation and composition post-adsorption determine the activation of the coagulation cascade, complement system, and immune cells (Gorbet and Sefton, 2004; Franz *et al*., 2011).

Recent studies have demonstrated that selective adsorption of plasma proteins is associated with the hydrophilicity and hydrophobicity of the graft surface (Moulod and Moghaddam, 2022). Albumin, which has a high proportion of charged residues, tends to adsorb to hydrophilic surfaces (Wu *et al*., 2021). Dabare *et al*. (2021) investigated differentiated human monocytic leukemia cells (dTHP-1) and found that the interaction of immune cells with surface-adsorbed albumin via scavenger receptors led to an overall decrease in pro-inflammatory markers and an increase in anti-inflammatory markers (Dabare *et al*., 2021). Surface models with varying chemistries, prepared by plasma polymerization, revealed that surfaces rich in positively charged amines and oxazolines resulted in the greatest albumin adsorption and conformational changes compared to surfaces rich in carboxylic acid groups and pure hydrocarbons (Dabare *et al*., 2022).

In contrast to albumin, the larger-sized Fg tends to diffuse on hydrophobic surfaces to achieve stable adsorption (Wu *et al*., 2021). Fg binds to hydrophobic surfaces through its relatively hydrophobic D and E regions, exposing the α C region to recruit other Fg molecules. This leads to the aggregation of Fg into larger fibers and the binding of platelets to form agglomerates, resembling the formation of blood clots catalyzed by thrombin, Ca^{2+}, and coagulation factor XIII (Wade *et al*., 2010; Zhang *et al*., 2017; Xu *et al*., 2022). However, this phenomenon does not occur on hydrophilic surfaces (Zhang *et al*., 2017). Fg plays a crucial role in hemostasis and coagulation, and its excessive recruitment to form thrombi can lead to the development of foreign body reactions post-transplantation. Considering the influence of graft surface hydrophilicity on the selective adsorption of plasma proteins, various substances have been applied to decellularized matrices to improve hydrophilicity and biocompatibility, such as N-(2-hydroxypropyl) propyl-3-trimethylchitosan ammonium chloride, epoxidized N-(2-hydroxypropyl)-3-trimethylchitosan ammonium chloride, and sodium hyaluronate (Zheng *et al*., 2021; Ding *et al*., 2022).

Ig, an antibody-active globulin, plays a role in complement activation and immunomodulation (Frischauf *et al*., 2021; Oskam *et al*., 2023). The pre-adsorption of Fg, Ig, platelet factors, and other serum proteins mediates the activation and adhesion of neutrophils, monocytes, and macrophages to the graft, leading to an early inflammatory response (Åsberg and Videm, 2005; Love and Jones, 2013). In 2023, Zhao *et al*. attributed the early immune recognition and subsequent osteoinduction after biphasic calcium phosphate implantation to the adsorption of proteins, primarily fibronectin (Fn) and high mobility group protein B1 (HMGB1) (Zhao *et al*., 2023). It was inferred that the selective adsorption of plasma proteins may modulate the immune response mediated by decellularized matrix grafts.

Immune cell populations are recruited and interact in a dynamic inflammatory microenvironment

Previous studies have demonstrated the presence of various immune cell populations (CD68+ macrophages, CD163+ macrophages, T lymphocytes, MHC class II-positive cells, mast cells, and NK cells) during the 112 days following decellularized matrix implantation in rats, with different temporal changes (Lucke *et al*., 2015). In 2022, Xu *et al*. showed that the local inflammatory micro-environment induced by decellularized matrix implantation evolves into two phases as the graft progresses: an acute inflammatory phase dominated by neutrophils and M1 macrophages, and a chronic inflammatory phase dominated by M2 macrophages and helper T2 (Th2) cells (Xu *et al*., 2022). The persistence, transformation, or exit of inflammatory cells at the transplant site may alter the fate of the graft (Xu *et al*., 2022).

During decellularized matrix transplantation, tissue or cell damage inevitably occurs, releasing damage-associated molecular patterns (DAMPs). DAMPs can be recognized by pattern-recognition receptors (PRRs), which serve as one of the main triggers for neutrophil migration to the site of injury (Love and Jones, 2013; Hu *et al*., 2021). The presence of chemokines secreted by neutrophils, such as chemokine ligand 1 (CXCL1), leukotriene B4 (LTB4), and complement fragment C5a, leads to the recruitment of more neutrophils and amplifies their response (Witte and Barbul, 1997; Kew, 2019; Antmen *et al*., 2021; Xu *et al*., 2022; Wang *et al*., 2023). Clinically, elevated neutrophil levels often indicate host tissue injury, acute infections, or septic infections.

Tissue-resident and peripheral blood-derived macrophages are recruited and polarized to the M1 phenotype by neutrophil-secreted pro-inflammatory factors, including IL-1, IL-12, TNF-α, interferon-γ (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Witherel *et al*., 2016; Masoomikarimi and Salehi, 2022; Xu *et al*., 2022). M1 macrophages express high levels of pro-inflammatory factors, such as IL-1β, IL-6, TNF-α, IFN-γ, GM-CSF, and inducible nitric oxide synthases (iNOs), which activate STAT1 and nuclear factor-κB (NF-κB) pathways (de Paula *et al*., 2023). These macrophages play a role in killing pathogens, phagocytosing cellular debris during the acute inflammatory phase, and promoting helper T cell (Th1) immune responses (Lucke *et al*., 2015).

In response to the inflammatory micro-environment in the late transplantation phase, macrophages polarize to the M2 phenotype, with a positive correlation observed between the number of T-lymphocytes and M2 macrophages (Lucke *et al*., 2015). M2 macrophages secrete cytokines, such as IL-10, TGF-β, and vascular endothelial growth factor (VEGF), which induce Th2 activation and favor the development of a pro-reconstructive micro-environment at the transplantation site. This process involves high expression of the peroxisome proliferator-activated receptor (PPAR) pathway, and fiber-forming factors in STAT6, arginase, and IL-10 (de Paula *et al*., 2023).

Polarization can be induced by different molecules for the four subtypes of M2 macrophages: M2a, M2b, M2c, and M2d (Masoomikarimi and Salehi, 2022). Witherel *et al*. (2016) labeled the M2a phenotype with the macrophage-derived chemokine (CCL22) and the macrophage mannose receptor 1 (MRC1) and labeled the M2c phenotype with the CD163

molecule to investigate the effect of commercially available decellularized matrices on macrophage phenotype. Current research suggests that M2a promotes ECM deposition and remodeling, while M2c has an anti-fibrotic effect. However, further research is needed to clarify the roles of the other phenotypes in the context of allogeneic or xenografts.

Macrophages coordinate tissue responses at all stages of graft integration, including the acute inflammatory stage, chronic inflammatory stage, and wound healing or foreign body reaction stage (Sadowska and Ginebra, 2020; Marques *et al*., 2021; Martin and Garcia, 2021; Rafikova *et al*., 2023). When macrophages of different origins (primary cultured macrophages and THP-1-derived macrophages) were cultured on a commercially available decellularized matrix (Integra Skin Regeneration Templates), differences in gene expression trends were observed. Primary cultured macrophages resulted in the upregulation of CD163 proteins, macrophage-derived chemokines, and matrix metalloproteinase inhibitor 3 compared to THP-1-derived macrophages (Witherel *et al*., 2016). However, primary cultured macrophages have limitations in terms of proliferative capacity and individual variability. Therefore, THP-1-derived macrophages appear to be more useful for predicting *in vivo* behavior.

Well integration of the decellularized matrix with the host tissue or the occurrence of a foreign body reaction reveals graft outcomes

The precise regulation of tissue integration and remodeling induced by decellularized matrices is orchestrated by immune cell populations. During the acute inflammatory phase, neutrophils and M1 macrophages predominate, degrading the matrix and clearing cellular and tissue debris. In the chronic inflammatory phase, M2 macrophages and Th2 cells prevail, promoting extracellular matrix (ECM) deposition and matrix remodeling (Xu *et al*., 2022). However, excessive matrix remodeling often results in a foreign body reaction and dysfunction, characterized by a fibrotic envelope (Yoo *et al*., 2023).

Fibrosis, the scarring and hardening of tissue due to excessive ECM deposition by myofibroblasts in response to chronic inflammation, is associated with various factors, including graft site, composition, and noxious stimuli during or after transplantation (Ueha *et al*., 2012). Deep dermis and fibroblasts exhibit more pro-fibrotic characteristics compared to superficial dermis and fibroblasts, while deep decellularized dermal matrices display fewer pro-fibrotic features than superficial dermal matrices (Zuo and Lu, 2017). In 2022, Wei *et al*. identified macrophage-to-myofibroblast transformation as a novel mechanism inducing renal fibrosis in response to chronic inflammation (Wei *et al*., 2022), potentially playing a similar role in fibrosis induced by decellularized matrix transplantation.

The key criterion for successful decellularized matrix transplantation is the ability to provide a framework for growth, integrate with host tissues, and replace the original tissues, restoring normal physiological function. Numerous reports have documented successful decellularized matrix transplantation in animal injury models (Huang *et al*., 2016; Van Eps *et al*., 2021). In 2023, Melkonyan *et al*. used porcine acellular dermal matrix (PADM) obtained through detergent-enzyme treatment for treating porcine hernia defects via the sublaminar method (Melkonyan *et al*., 2023). Histological examination of 60-day postoperative biopsy specimens revealed PADM replacement by newly formed connective tissues and well-remodeled tissue. Notably, the PADM size and shape were determined by rapid modeling of the defect site during surgery rather than using a fixed PADM shape, an innovative approach potentially contributing to personalized medicine development (Melkonyan *et al*., 2023).

Decellularized matrices have enabled long-term transplantation and tissue integration in clinical trials across various areas, such as nasal mucosal repair (Bing *et al*., 2019), blepharoplasty (Huang *et al*., 2022), breast reconstruction (Broyles *et al*., 2021), and full-layer chest wall defects (Heo *et al*., 2022). However, fewer reports exist for defects involving whole skin tissue with bone, tendon, and muscle growth. In 2019, Jackson and Roman performed staged debridement and temporary coverage using a cadaveric skin-derived decellularized dermal matrix on a patient with full-thickness facial burns, providing early evidence for decellularized matrix use in such cases (Jackson and Roman, 2019). In 2023, Li *et al*. recruited 7 patients with total skin defects of the lower extremities and achieved complete wound healing within 20 weeks using the decellularized dermal matrix product Pelnac without requiring flaps or skin grafts, suggesting the suitability of decellularized matrices for uninfected, non-ischemic, and total skin defect wounds (Li *et al*., 2023).

IMMUNE SIGNALING IN DECELLULARIZED MATRIX TRANSPLANTATION

Toll-like receptors and immune recognition

Toll-like receptors (TLRs), key members of pattern recognition receptors (PRRs), are predominantly expressed in myeloid immune cells, particularly macrophages. TLRs recognize residual immunogenic components of the decellularized matrix, such as bacterial cytoplasm and viral products, and are centrally involved in initiating both innate and adaptive immune responses post-transplantation. Among the 10 identified human TLR family members, TLR4 and TLR9 have been extensively studied in decellularized matrix transplantation (Mishra and Pathak, 2019).

To date, researchers have identified 10 TLR family members in humans, among which TLR4 and TLR9 have been more extensively studied in the context of decellularized matrix transplantation. TLR4, localized on the surface of cell membranes, primarily recognizes microbial membrane components, including peptidoglycan (Jian *et al*., 2019), lipopolysaccharide (Valdes-Lopez *et al*., 2022), flagellin (Zhou *et al*., 2020b), etc. Studies have shown that bladder-decellularized matrices exhibit higher TLR4 expression levels, potentially detrimental to tissue regeneration. Fortifying bladder-decellularized matrices with hyaluronic acid and VEGF can regulate the host immune response and promote regeneration by decreasing TLR4 and IL-4 while increasing TGF-β1 (Evren *et al*., 2010). Additionally, purified adipose-derived stem cells (ADSCs) can inhibit the expression of TLR4-associated inflammatory proteins (e.g., macrophage antigen-1, myeloid differentiation factor 88 (MYD88), NF-κB, IL-6, and TNF-α), exerting an immunomodulatory effect (Wang *et al*., 2018).

TLR9, distributed in intracellular compartments such as lysosomes and endoplasmic reticulum, recognizes pathogen-derived nucleic acids or nucleic acids in disease conditions (Kawasaki and Kawai, 2014; Duan *et al*., 2022), including dou-

ble-stranded RNA (Croes *et al*., 2019), single-stranded RNA (Shafeghat *et al*., 2022), short interfering RNA (Shafeghat *et al*., 2022), as well as RNA-DNA hybrids (Obermann *et al*., 2019), etc. Vasanthan *et al*. (2023) demonstrated that epicardial implantation of porcine small intestinal submucosa extracellular matrix (SIS-ECM) increased fibroblast transcription and angiogenesis of inflammatory pathways through a TLR9-dependent pathway and fibroblast growth factor 2 (Vasanthan *et al*., 2023). In contrast to the immune-recognition function of TLR1-9, Hess and Nicholas James present evidence that TLR10 acts as a suppressor of the inflammatory response and is a potential therapeutic target for addressing chronic inflammatory diseases (Hess *et al*., 2017).

Graft-induced TLR signaling is primarily mediated through the MYD88-dependent pathway (Shen *et al*., 2012; Biguetti *et al*., 2016). Upon recognition of the corresponding immunogenic component by the TLR extracellular segment, the intracellular segment undergoes a conformational change, recruiting MYD88. This initiates downstream signaling via tumor necrosis factor receptor-associated factor 6 (TRAF6) and activates the NF-κB pathway, leading to the production of pro-inflammatory or anti-viral cytokines and chemokines, such as IL-6, IL-8, IL-12, and TNF-α (Shen *et al*., 2012; Duan *et al*., 2022). Furthermore, MYD88 may be involved in signaling related to macrophage polarization in response to graft pore size (Medzhitov *et al*., 1998; Duan *et al*., 2022). The surface accessible area size of the grafts can successively affect the exposure rate of cysteine residues in HMGB1, TLR4 activation, and thus modulate MyD88-TRAF6 and NF-κB signaling (Zhang *et al*., 2022). At this stage, macrophage-based antigen-presenting cells complete antigen recognition and processing, highly express MHC molecules, and present antigens to T cells to further elicit immune response effects.

T cell receptors and T cell activation

T cell receptors (TCRs) are molecular structures on T cells that specifically recognize and bind MHC/antigen peptides on the surface of antigen-presenting cells, playing a major role in cell-mediated immune responses (Knapp and Deane, 2016; Zajonc, 2020). The CD3 molecule, a common marker on the surface of all T-cells (helper T-cells/CD4+ T-cells, cytotoxic T-cells/CD8+ T-cells, regulatory T-cells (Treg), and natural killer T-cells (NKT-cells), typically forms a complex with the T-cell receptor (TCR), providing the initial signal required for T-cell activation. Upon receiving additional stimulatory signals, T cells become activated, proliferate, and differentiate into effector and memory cells, releasing perforin and immunoreactive substances to perform target cell killing, immunomodulation, and immune memory functions.

T-cell surface molecules, including CD3, CD11, and CD31, are involved in the immune response following decellularized matrix implantation, with CD3 commonly used as an indicator of inflammatory response intensity (Shirani *et al*., 2021; Nahabedian *et al*., 2023; Yoo *et al*., 2023). Bernardini *et al*. (2020) demonstrated that implantation of bovine decellularized pericardial biologic mesh decreased peritoneal α-smooth muscle actin (α-SMA) expression and CD3+ inflammatory cell infiltration while increasing capillary density and cellular proliferation; however, the mesh structure significantly impacted post-implantation tissue remodeling (Bernardini *et al*., 2020). Woo *et al*. (2021) showed, using CD3 staining, that irradiation sterilization plays a crucial role in the inflammatory response induced by acellular dermal matrix (ADM) implantation in mice, with more persistent irradiation leading to reduced collagen fiber deposition and an inflammatory response in the skin (Woo *et al*., 2021). Wang *et al*. (2021) implanted porous ACM and ADM into goat subcutis, demonstrating that ADM expressed higher levels of cartilage-related genes (ACAN, COLIIA1, SOX9, etc.) and lower immune responses (CD3, CD68) compared to ACM (Wang *et al*., 2021).

Decellularized matrices have been shown to regulate T cell-macrophage interactions. Methoxy polyethylene glycol-modified acellular adipose matrix (AAM) increased the number of Treg cells and enhanced the M2/M1 macrophage ratio through the secretion of IL-2, IL-1, and TGF-β10, effectively reducing the immunogenicity of xenografted AAM (Liu *et al*., 2021a). HE *et al*. (2020) found that decellularized sheep periosteum did not induce severe immunogenic responses through the Th1 pathway compared to fresh sheep periosteum.

In summary, after recognizing immunogenic components in decellularized matrix grafts, macrophage-based antigen-presenting cells highly express MHC molecules through the TLR/MYD88 signaling pathway, binding to the TCR-CD3 complex to complete antigen presentation and provide the initial signal for T-cell activation, mediating the subsequent immune response (Fig. 3). The crosstalk between macrophages and T cells contributes to further immune cell activation and immune response regulation, warranting more in-depth studies to clarify their interaction mechanism.

TGF-β/SMAD signaling and tissue repair

The primary functions of the immune system are to defend against foreign pathogens and maintain the host's internal homeostasis. The TGF-β family, which consists of key immunomodulators, plays a vital role in coordinating various immune system functions that encompass a wide range of physiological processes, such as cellular behavior, ECM deposition, and tissue repair and regeneration (Xu *et al*., 2022).

TGF-β/Smad signaling plays a pivotal role in decellularized matrix-mediated ECM deposition and tissue repair (Chen *et al*., 2017; Alemzadeh *et al*., 2020; Lin *et al*., 2020; Yang *et al*., 2021). In 2020, Hu *et al*. showed that human umbilical cord MSCs loaded with decellularized renal scaffolds restored renal function and reduced fibrosis by decreasing epithelial-mesenchymal transition through the TGF-β/Smad signaling pathway in subtotal nephrectomized rats (Hu *et al*., 2020). Tilapia-skin decellularized dermal matrix significantly promoted granulation growth, collagen deposition, angiogenesis, and re-epithelialization, possibly due to the high expression of TGF-β1, α-SMA, and CD31 (Li *et al*., 2021). Naringin may promote the repair of cartilage defects in combination with the decellularized dermal matrix by activating the TGF-β/TGFβ type I receptor kinase (ALK5)/Smad2/3 signaling pathway, resulting in high expression of TGF-β2, TGF-β3, and Sox-9 (Ye *et al*., 2022).

Researchers often transplant decellularized matrices in combination with TGF-β to promote ECM remodeling and regeneration. Liu *et al*. (2021b) doped VEGF and TGF-β1 into a silk protein film and sandwiched the membrane into a bilayer of decellularized mucosal submucosa of the porcine small intestine to form a nucleus-shell structure, which was shown to stably induce ECM remodeling in response to a milder xenobiotic response (Liu *et al*., 2021b). In combination with TGF-β1, autologous adipose-derived MSCs with allogenic de-

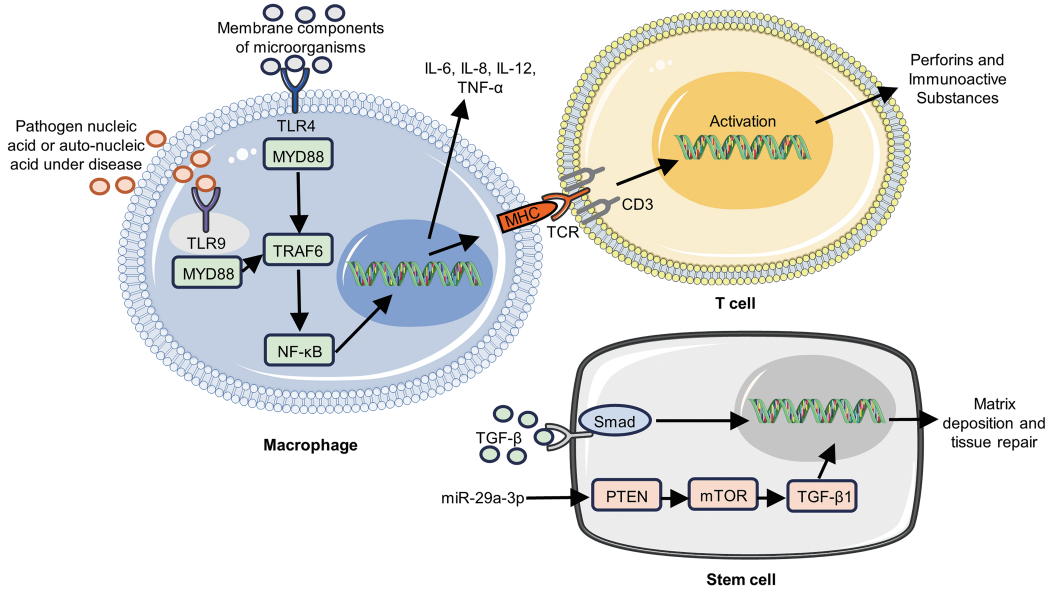

Fig. 3. The immunologic mechanisms following decellularized matrix transplantation involve several crucial steps. (i) During the immune recognition phase, Toll-like receptor 4 (TLR4) primarily recognizes membrane components of microorganisms, while TLR9 recognizes nucleic acids from pathogens or disease conditions. Both receptors utilize the adaptor protein MYD88 for intracellular signaling and upregulate the expression of major histocompatibility complex (MHC) molecules to facilitate antigen recognition and processing. (ii) The T-cell receptor (TCR)-CD3 complex specifically recognizes MHC molecules, providing the "first signal" of the dual signals required for initiating T-cell activation, which results in a regulated immune response. (iii) The transforming growth factor-β (TGF-β)/SMAD signaling pathway is a key regulator of decellularized matrix-mediated ECM deposition. Recent studies suggest that miR-29a-3p may improve transplantation outcomes by modulating the TGF-β pathway.

cellularized neural matrix grafts were sufficient to support the regeneration of 50 mm sciatic nerve defects (Luo *et al*., 2012). When oral keratinocytes and TGF-β1 siRNA-transfected fibroblasts were inoculated onto sterilized bladder decellularized matrix, TGF-β1 siRNA decreased the expression of type I collagen synthesized by fibroblasts and facilitated the acquisition of tissue-engineered mucosa for urethral reconstruction (Li *et al*., 2013).

Exosomes, an emerging nanoscale decellularization therapy, can be used for targeted delivery of proteins, mRNAs, miRNAs, and other substances, potentially enabling tissue repair through the TGF-β pathway. Yao *et al*. (2021) found that human umbilical cord mesenchymal stem cell-derived exosomes (HUMSC-Exos) enhanced tendon-specific matrix components in a rat tendon injury model, noting that miR-29a-3p significantly increased in HUMSC-Exo-treated tendons and identifying phosphatase and tensin homolog (PTEN) as a specific target of miR-29a-3p. PTEN expression was downregulated in HUMSC-Exos-treated tendon-derived stem cells (TDSC) and reversed by miR-29a-3p antagonists. As PTEN is a key negative regulator of the mammalian target of rapamycin (mTOR) signaling, HUMSC-Exos overexpressing miR-29a-3p significantly increased the expression of tendon markers and the level of p-mTOR in TDSC, whereas rapamycin, an mTOR pathway inhibitor, significantly inhibited these properties. Thus, HUMSC-Exos may improve tendon healing by activating the mTOR pathway. HUMSC-Exos significantly increased TGF-β1 production in TDSC, and miR-29a-3p overexpression enhanced these effects, while the TGF-β1 inhibitor significantly suppressed HUMSC-Exo-mediated changes in the expression levels of decorin, scleraxis, and collagen. Collectively, the PTEN/mTOR/TGF-β1 signaling cascade may be a key signal for HUMSC-Exos-mediated delivery of miR-29a-3p to promote tendon healing (Yao *et al*., 2021).

MiR-29a-3p can serve as a marker for muscle repair and recovery from damage (Håkansson *et al*., 2018). In patients with gluteal myoclonus, miR-29a-3p negatively regulates TGF-β1 expression by binding to the 3' UTR region of SERPINH1 (Zhou *et al*., 2020a). However, in fibrotic diseases, TGF-β inhibits miR-29 family expression, resulting in increased ECM collagen formation. Upregulation of the miR-29 family contributes to the inhibition of fibrosis development (Dalgaard *et al*., 2022). Previous evidence suggests that TGF-β/Smad signaling is an important factor in decellularized matrix-mediated ECM deposition and tissue repair (Yang *et al*., 2021). Therefore, it is reasonable to hypothesize that the crosstalk between miR-29a-3p and TGF-β signaling may play a role in decellularized matrix-mediated tissue remodeling or fibrosis. However, more in-depth reports are lacking, and further studies are needed to clarify the mechanism of miRNA action in decellularized matrix transplantation.

SUMMARY AND OUTLOOK

Decellularized matrices have great potential for application in tissue defect repair due to their unique bio-activity and low immunogenicity. For human subjects, human-derived decellularized matrices are severely restricted in terms of ethics, source, and cost; therefore, allogenic decellularized matrices are widely favored. However, immunogenic components such as α-Gal epitopes, MHC molecules, collagen type I, col-

lagen type V, and k-α 1 microtubule proteins tend to trigger adverse host immune responses. To improve transplantation outcomes, the use of knockout animals can reduce immunogenicity at the source, and chemical and enzyme-linked decellularization techniques contribute to a safe decellularization process. The further development of PIAS1 and other markers may help effectively predict graft outcomes in the decellularized matrix.

In this paper, we summarize the host immune response induced by decellularized matrix transplantation into three chronological parts: (i) selective adsorption of plasma proteins on the decellularized matrix surface, with albumin tending to adsorb on hydrophilic surfaces and fibrinogen readily adsorbing on hydrophobic surfaces. TLR signaling plays a critical role, and MYD88 may respond to the decellularized matrix surface properties, participating in macrophage polarization. TLR10 may be a potential therapeutic target for addressing chronic inflammation in the future; (ii) recruitment and interaction of immune cell populations, dominated by neutrophils, macrophages, and T cells, in a dynamic inflammatory microenvironment consisting of two main phases: an acute inflammatory response dominated by neutrophils and M1 macrophages, followed by a chronic inflammatory response stage dominated by M2 macrophages and Th2 cells. The decellularized matrix can regulate the crosstalk between macrophages and T cells, with TCR signaling providing the initial signal for T cell activation and CD3 reflecting the inflammatory response strength; (iii) well integration of the decellularized matrix with the host tissue or the occurrence of a foreign body reaction reveals graft outcomes, with TGF-β/SMAD signaling as a key regulator at this stage. Transplantation of decellularized matrix in combination with TGF-β promotes ECM deposition and tissue regeneration, and miR-29a-3p may promote tissue repair through TGF-β1 signaling.

In the future, heterologous decellularized matrices will have a wider range of applications, and the immunological mechanisms mediated by decellularized matrix transplantation will be a focus of research. The interaction between macrophages and T cells contributes to immune regulation. The development of predictive markers for transplantation outcomes and therapeutic targets for adverse outcomes is important, and the role of miRNAs in promoting tissue repair and improving transplantation outcomes should be further explored.

CONFLICT OF INTEREST

The authors declare no competing interest.

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