

Review

Biomaterials for Vascular Reconstruction: Present Challenges and Future Perspectives

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Abstract:

Decellularized vascular scaffolds represent a promising strategy in vascular tissue engineering because they aim to remove cellular and nuclear material while preserving the extracellular matrix (ECM) architecture, biochemical composition, and mechanical properties of native vessels. However, decellularization is inherently a balance between effective cell removal and preservation of matrix integrity, since physical, chemical, and enzymatic treatments can alter ECM ultrastructure, surface composition, and biological activity (Gilbert et al., 2006; Crapo et al., 2011). Although decellularized vascular matrices provide a biologically active scaffold that can support cell adhesion, remodeling, and tissue integration, their clinical performance remains limited by thrombosis, insufficient endothelialization, intimal hyperplasia, and long-term patency challenges (Moroni & Mirabella, 2014; Li Y. et al., 2023). This review summarizes traditional methods for vascular scaffold decellularization and discusses current evaluation criteria, including residual DNA removal, ECM preservation, mechanical competence, hemocompatibility, and endothelialization potential. Particular attention is given to emerging approaches such as non-thermal irreversible electroporation (NTIRE), which may assist cellular disruption while reducing chemical damage, and cold plasma functionalization, which may improve scaffold surface wettability, bioactivity, and cell–matrix interactions (Phillips et al., 2010; Lombardo et al., 2024). Finally, the review considers the future potential of combining electroporation-assisted decellularization with plasma-based surface functionalization to improve vascular scaffold preparation, luminal endothelialization, and blood-contacting performance.

Keywords: Vascular scaffolds; Decellularization; Extracellular matrix; Electroporation; Plasma functionalization; Endothelialization; Tissue engineering

1. Introduction

Cardiovascular tissue engineering aims to develop vascular substitutes that can restore blood flow while preserving mechanical stability, hemocompatibility, and biological integration. Although autologous vessels remain the preferred option for many bypass procedures, they are not always available in sufficient quality or length. Synthetic vascular grafts are clinically useful in large-diameter vessels, but their performance remains limited in small-diameter applications, where thrombosis, restenosis, poor endothelial recovery, and compliance mismatch contribute to graft failure (Moroni and Mirabella, 2014; Ren et al., 2015; Li Y. et al., 2023).

Decellularized vascular scaffolds have therefore gained attention as biological alternatives to synthetic conduits. Decellularization aims to remove cellular and nuclear material, which may contain immunogenic donor antigens, while preserving the extracellular matrix (ECM), the three-dimensional network of proteins and polysaccharides that provides structural support and biochemical signals to cells. Unlike inert materials, the ECM can influence cell adhesion, migration, proliferation, differentiation, and tissue remodeling, making it an active biological microenvironment rather than a passive support structure (Gilbert et al., 2006; Crapo et al., 2011). In vascular scaffolds, this retained matrix is particularly valuable because it can preserve vessel-like architecture and provide cues for host cell repopulation, endothelialization, and integration (Moroni and Mirabella, 2014; Li J. et al., 2023).

However, decellularization alone is not sufficient to ensure graft function. Small-diameter vascular scaffolds are directly exposed to circulating blood, and the absence of a continuous endothelial lining can expose thrombogenic ECM components, allowing platelet adhesion, clot formation, reduced perfusion, and tissue damage. For this reason, re-endothelialization of the luminal surface is a central requirement for long-term patency and functional vascular regeneration (Mazloomnejad et al., 2023). At the same time, conventional decellularization protocols based on detergents, enzymes, osmotic treatments, and physical disruption may damage ECM ultrastructure, alter surface properties, or reduce biological cues needed for later cell attachment (Gilbert et al., 2006; Crapo et al., 2011).

These limitations have encouraged interest in emerging and complementary strategies. Non-thermal irreversible electroporation (NTIRE), an electrical method that disrupts cell membranes while aiming to limit thermal and chemical damage, has been investigated as a potential physical adjunct for vascular decellularization (Phillips et al., 2010). In parallel, cold plasma functionalization has been explored as a post-decellularization surface treatment capable of modifying wettability and surface chemistry to improve cell–material interactions, although vascular-specific validation remains limited (Lombardo et al., 2024). This review therefore examines traditional vascular scaffold decellularization, scaffold evaluation criteria, electroporation-assisted approaches, plasma functionalization, and the future potential of combining these strategies to improve vascular scaffold performance.

2. Traditional Methods for Vascular Scaffold Decellularization

Traditional vascular scaffold decellularization usually combines physical, chemical, and enzymatic approaches because no single method can reliably remove cellular material while fully preserving extracellular matrix (ECM) structure. Physical methods, such as freeze–thawing, agitation, pressure, and sonication, can disrupt cell membranes and improve reagent penetration, but they are rarely sufficient as stand-alone techniques. Therefore, they are commonly combined with detergents, enzymes, chelating agents, nucleases, and extensive washing steps to remove cellular debris and residual reagents (Gilbert et al., 2006; Crapo et al., 2011).

Chemical methods remain central to most vascular decellularization protocols. Detergents are particularly important because they solubilize cell membranes and help remove cytoplasmic and nuclear components. However, their effectiveness must be balanced against possible damage to ECM proteins and bioactive molecules. Ionic detergents such as sodium dodecyl sulfate (SDS) and sodium deoxycholate are effective for removing cells and nucleic acids, but they can disrupt collagen organization, reduce glycosaminoglycans (GAGs), and alter vascular microstructure. In contrast, non-ionic detergents such as Triton X-100 are generally milder and may better preserve protein-rich ECM structures, although they may be less effective for complete decellularization when used alone (Gilbert et al.,

2006; Li J. et al., 2023; Mazloomnejad et al., 2023). Zwitterionic detergents such as CHAPS, or 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate, have also been used because they may preserve collagen, elastin, and GAGs better than stronger ionic detergents, although their effects remain protocol-dependent (Li J. et al., 2023).

Enzymatic treatments can further assist decellularization. Trypsin may help detach cells from the ECM and improve the penetration of later reagents, while deoxyribonuclease and ribonuclease, commonly abbreviated as DNase and RNase, degrade residual nucleic acids. Nevertheless, enzymatic exposure must be carefully controlled, since prolonged digestion can damage laminin, fibronectin, elastin, collagen networks, and other matrix components required for endothelial cell attachment and vascular function (Gilbert et al., 2006; Moroni and Mirabella, 2014).

For vascular tissues, perfusion-based decellularization is particularly relevant because the native vascular lumen can be used to deliver reagents more uniformly through the scaffold. Compared with simple immersion or diffusion-based methods, perfusion can improve detergent distribution, cellular debris removal, and preservation of vessel architecture and patency (Crapo et al., 2011; Mazloomnejad et al., 2023). Overall, traditional vascular decellularization should be understood as a tissue-specific optimization process. The selected protocol must remove cellular and nuclear material while preserving ECM architecture, mechanical behavior, and the surface features needed for later endothelialization and hemocompatibility (Li Y. et al., 2023; Moroni & Mirabella, 2014).

3. Evaluation of Decellularized Vascular Scaffolds

The evaluation of decellularized vascular scaffolds should confirm not only the removal of cellular material, but also the preservation of the extracellular matrix (ECM) features required for vascular function. Commonly used criteria for effective decellularization include residual double-stranded DNA (dsDNA) below 50 ng/mg dry ECM, DNA fragments shorter than 200 base pairs, and absence of visible nuclear material after hematoxylin and eosin (H&E) or 4',6-diamidino-2-phenylindole (DAPI) staining (Crapo et al., 2011). However, DNA removal alone does not fully define scaffold quality. Residual cellular proteins, xenogeneic antigens such as α -Gal, N-glycolylneuraminic acid (Neu5Gc), SDa antigen, and major histocompatibility complex (MHC) molecules may also influence host responses and should be considered when evaluating biological compatibility (Li Y. et al., 2023).

Because vascular scaffolds must withstand blood pressure and surgical manipulation, ECM preservation and mechanical competence are equally important. Collagen and elastin integrity should be assessed because collagen contributes to tensile strength, while elastin supports vessel recoil and compliance. Other ECM molecules, including laminin, fibronectin, glycosaminoglycans (GAGs), and basement membrane collagen IV, are also relevant because they support endothelial cell adhesion, migration, and re-endothelialization (Gilbert et al., 2006; Moroni & Mirabella, 2014; Mazloomnejad et al., 2023). Therefore, vascular scaffold evaluation should include mechanical tests such as burst pressure, compliance, tensile strength, and suture retention strength, together with histological and biochemical analysis of ECM structure.

Functional testing is especially important for vascular applications. Even a scaffold that meets decellularization criteria may fail if it promotes thrombosis or does not support endothelial coverage. Evaluation should therefore include platelet adhesion, clotting behavior, hemolysis, endothelial cell attachment, proliferation, spreading, and the ability to form a confluent endothelial layer on the luminal surface (Ren et al., 2015; Li J. et al., 2023). For modified scaffolds, additional tests are required. For example, plasma-functionalized decellularized ECM materials should be assessed for surface chemistry, wettability, cell adhesion, hemocompatibility, and mechanical preservation, while electroporation-treated arteries should be evaluated for cellular loss together with collagen, elastin, and luminal endothelial recovery (Phillips et al., 2010; Lombardo et al., 2024). Overall, scaffold evaluation must integrate structural, biochemical, mechanical, immunological, and blood-contacting criteria to determine whether the final vascular matrix is suitable for regeneration.

4. Future Perspectives of Decellularized Vascular Scaffolds

Future vascular scaffold preparation will likely require multi-step protocols that address cell removal, extracellular matrix (ECM) preservation, and luminal surface optimization as connected but distinct objectives. Traditional decellularization methods can effectively remove cellular and nuclear material, but chemical, enzymatic, and physical treatments may also disrupt ECM architecture, reduce glycosaminoglycans (GAGs), alter adhesive proteins, and affect the mechanical or biological properties of the scaffold. Therefore, future protocols should be tissue-specific and should use the mildest effective strategy capable of achieving adequate decellularization while preserving collagen, elastin, basement membrane structure, and matrix cues required for endothelialization and remodeling (Gilbert et al., 2006; Crapo et al., 2011).

Within this framework, non-thermal irreversible electroporation (NTIRE) may serve as a physical cell-disruption step. NTIRE uses short electrical pulses to destabilize cell membranes and induce irreversible membrane defects, leading to cell death without directly digesting the ECM. Experimental arterial studies have shown that NTIRE can produce markedly decellularized arterial segments while preserving detectable collagen and elastin structures, suggesting potential value for vascular scaffolds where matrix integrity is essential (Phillips et al., 2010). However, NTIRE should currently be considered an experimental adjunct rather than a complete replacement for conventional decellularization. Its effectiveness depends on pulse parameters, electrode geometry, treatment volume, thermal control, and the removal of cellular debris after membrane disruption. For this reason, future protocols may combine electroporation with perfusion, washing, or mild chemical pretreatment to improve debris removal while limiting ECM damage (Crapo et al., 2011; Koo et al., 2022).

Cold plasma functionalization may complement this approach by addressing the post-decellularization surface. After cellular removal, vascular scaffolds may retain native-like matrix architecture but still present a luminal surface that is not optimal for blood contact or endothelial cell attachment. Plasma treatment can modify surface wettability, introduce reactive chemical groups, and improve cell-material interactions without necessarily altering bulk scaffold mechanics. Lombardo et al. (2024) showed that nitrogen/hydrogen (N_2/H_2) cold plasma treatment of decellularized ECM films increased nitrogen- and oxygen-containing functional groups, improved hydrophilicity, enhanced early cell adhesion and proliferation, and maintained tensile properties, although the study was performed on bovine pericardium dECM films rather than tubular vascular grafts (Lombardo et al., 2024). In vascular applications, plasma-based surface modification may be particularly relevant because surface chemistry influences protein adsorption, platelet adhesion, endothelial cell behavior, and hemocompatibility (Ren et al., 2015; Li Y. et al., 2023).

Electroporation and plasma functionalization should therefore be viewed as potentially complementary rather than competing strategies. Electroporation could assist cellular disruption while reducing reliance on harsh detergents, whereas plasma functionalization could tune the preserved luminal ECM surface to improve wettability, endothelial attachment, and blood compatibility. Such a sequential approach remains hypothetical and requires direct vascular-specific validation. Future studies should evaluate whether electroporation-assisted decellularization followed by plasma functionalization improves residual DNA removal, ECM preservation, mechanical behavior, platelet interaction, endothelial cell coverage, and long-term graft patency. If successful, this integrated strategy could shift vascular scaffold preparation from simple cell removal toward a more functional approach combining gentle decellularization, surface bioactivation, and regenerative vascular remodeling (Moroni & Mirabella, 2014; Mazloomnejad et al., 2023).

5. Conclusions

Decellularized vascular scaffolds should be viewed not simply as acellular tubes, but as biologically active matrices whose function depends on preserved extracellular matrix (ECM) structure, reduced immunogenicity, mechanical competence, hemocompatibility, and restoration of a functional endothelial lining. Traditional decellularization protocols can effectively remove cellular and nuclear material, but they must be optimized for each tissue because physical, chemical, and enzymatic treatments may also alter collagen, elastin, glycosaminoglycans (GAGs), adhesive proteins, and growth factors that are

essential for scaffold bioactivity and vascular mechanics (Gilbert et al., 2006; Crapo et al., 2011; Moroni & Mirabella, 2014).

The major challenge for decellularized vascular matrices remains the translation from a structurally preserved scaffold to a functional blood-contacting graft. In particular, small-diameter vascular grafts continue to face limitations related to thrombosis, intimal hyperplasia, calcification, incomplete endothelialization, and long-term patency (Li Y. et al., 2023; Li J. et al., 2023). Therefore, future scaffold development should integrate objective decellularization criteria with functional evaluation of mechanical properties, platelet interaction, endothelial cell attachment, and in vivo performance.

Emerging strategies such as non-thermal irreversible electroporation (NTIRE) and cold plasma functionalization may contribute to this next generation of vascular scaffolds. NTIRE may assist cellular disruption while limiting damage to key ECM components, whereas plasma treatment may tune the luminal surface to improve wettability, cell-matrix interactions, and hemocompatibility (Phillips et al., 2010; Lombardo et al., 2024). However, both approaches require further vascular-specific validation. Overall, the future of decellularized vascular scaffolds will likely depend on integrated, multi-step protocols that combine gentle decellularization, preserved matrix mechanics, surface functionalization, and rapid re-endothelialization to create a stable, non-thrombogenic, and regenerative vascular interface (Ren et al., 2015; Mazloomnejad et al., 2023).

Conflicts of Interest: The authors declare no conflict of interest.

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