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Human pericardial extracellular matrix: An implantation platform for cardiac tissue engineering

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Tissue engineering, which involves the use of therapeutic biologicals supported by implantable materials, represents a promising tool to repair damaged tissues or organs. Among the most proper supporting materials and scaffolds, natural extracellular matrix (ECM) constitutes a dynamic platform of structural and functional fibers and biomolecules that confers a suitable microenvironment for cell attachment, proliferation and differentiation *via* activation of host signaling cues. In this context, ECM derived from human pericardium emerges as a supportive porous biomaterial to regenerate post-infarcted myocardium. In specific, pericardial ECM highlights as a potential clinical option for administering those active components grown and purified from large-scale cell cultures, such as mesenchymal stromal cells and derived extracellular vesicles, and to locally generate a vascularized bioactive niche promoting modulation of post-ischemic inflammation and cardiac repair.

KEYWORDS

pericardium, decellularization, extracellular matrix, mesenchymal stromal cells, extracellular vesicles, cardiac tissue engineering, cardiac repair

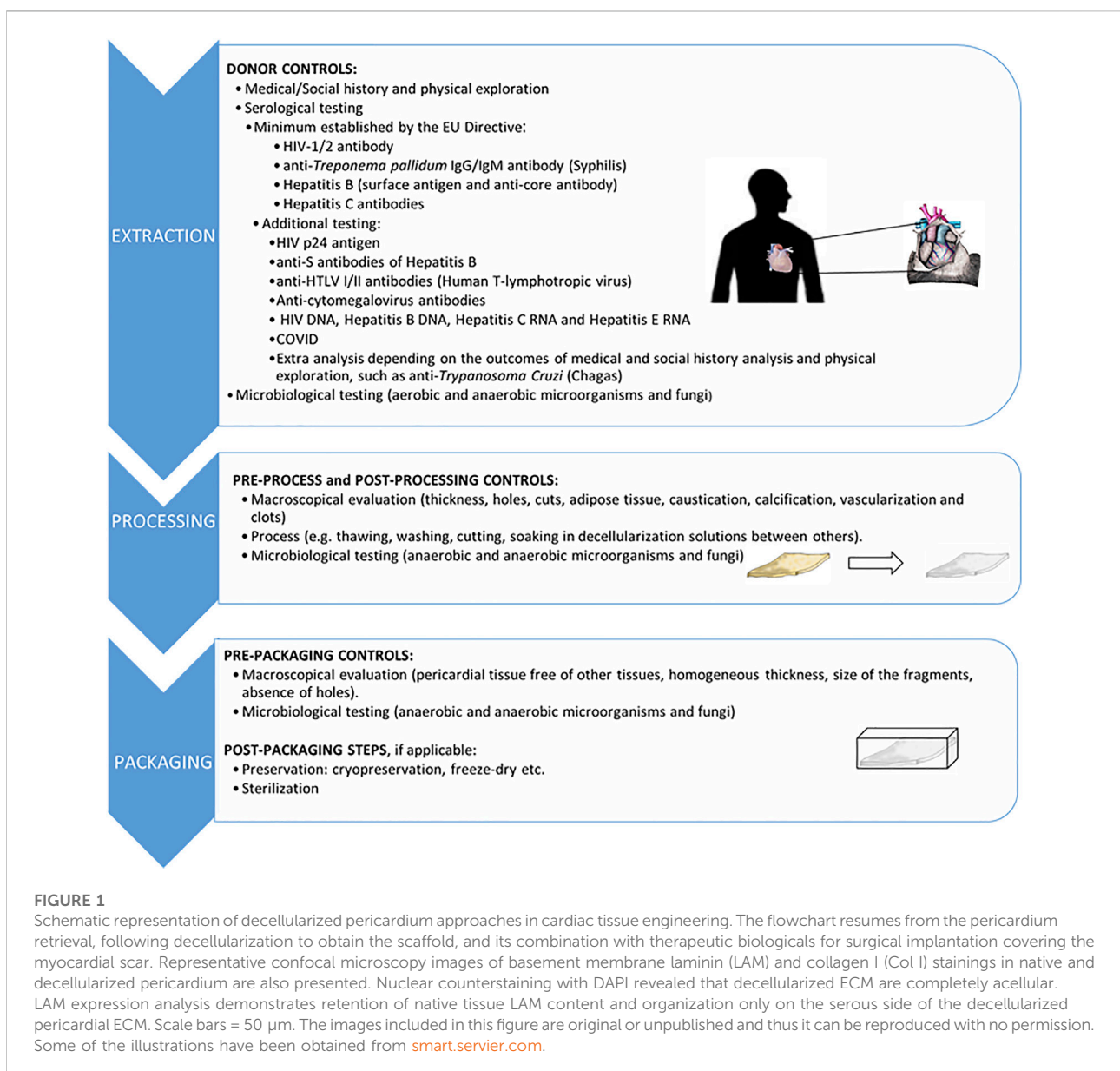
Abbreviations: 3-D, three-dimensional; Col I, type I collagen; ECM, extracellular matrix; EV, extracellular vesicles; bFGF, basic fibroblast growth factor; GMP, good manufacturing practices; GTP, good tissue practices; IMP, investigational medicinal product; LAM, laminin; MI, myocardial infarction; MSC, mesenchymal stromal cells; TE, tissue engineering.

Introduction

Myocardial ischemia, which is caused by coronary artery occlusion, leads to severe blood supply reduction and necrosis of cardiac tissue. Current treatments mainly focus on restoration of blood flow, increasing patients' life quality and expectancy, but do not address the complete recovery of the scarred tissue. Alternatively, cardiac tissue engineering (TE) has emerged as an advanced therapeutic option with engineering innovations that hold promise for clinical use (Castells-Sala et al., 2013). To that end, efforts have been made to develop scaffolding materials that mimic the native three-dimensional (3-D) cardiac tissue architecture and promote a viable microenvironment for regenerative cell attachment, proliferation, and differentiation

(Badylak et al., 2011; Castells-Sala and Semino, 2012). In general, the ideal TE material should be biodegradable and biocompatible, allowing tissue revascularization and triggering low inflammatory response within the tissues to be substituted or repaired (Loh and Choong 2013; Grigorian Shamagian et al., 2019). Moreover, cardiac grafts are needed to empower electrical and mechanical coupling with remaining host tissue increasing cardiac function output following myocardial infarction (MI) (Vunjak-Novakovic et al., 2010).

Inner body membranes, which comprise thin sheets or layers of cells covering the surface of internal organs, the outside of the body and lines various body cavities, are good candidates to be used as versatile tools in TE applications. In particular, these membranes are classified into two main categories which are



epithelial membranes (amniotic membrane, mesentery, omentum, pericardium, peritoneum, and pleura) and connective tissue membranes (fascia, periosteum, and synovial membrane). In comparison with synthetic materials, these biological membranes have better biocompatibility, less cytotoxicity and induce lower inflammatory reactions (Inci et al., 2020). They also have unquestionable advantages such as their natural hemodynamic resistance, absence of anticoagulant therapy and reduction of the risk of thromboembolic complications and anticoagulant-related hemorrhage (Grebenik et al., 2020). In this context, pericardium is a conical double-walled sac of fibrous tissue that surrounds the heart and the roots of the great blood vessels. The pericardial membrane is composed of an epithelium and connective tissue rich in collagen, glycoproteins and glycosaminoglycans, which mechanically stabilizes and protects the heart, and maintains cardiac geometry and pressure-volume relationships of the cardiac chambers (Rodriguez and Tan 2017). Pericardium can be used as a good scaffolding material providing a 3-D structure and promoting a viable microenvironmental in cardiac tissue engineering through different approaches (Figure 1). As previously described in bovine pericardium, human pericardium exhibits anisotropy of its surface ECM niches, with the serous layer (i.e., parietal pericardium) containing mostly basement membrane components (e.g., laminin, LAM) and the fibrous layer (i.e., mediastinal surface) being composed primarily of type I collagen (Col I) (Xing et al., 2021) (Figure 1).

Clinically, pericardial tissue from both human and xenogeneic origins has widely been used in the context of both cardiac and non-cardiac surgeries. In brief, pericardium grafts have been applied to correct intracardiac and diaphragm defects (Ricci et al., 2014; Yaliniz et al., 2014; Ascaso et al., 2021), as well as ischemic ventricular septal defect after acute MI (Mihalj et al., 2022). On the other hand, non-cardiac pericardium-based applications include replacement of brain dura mater (Sun et al., 2018), bleb repair, conjunctival reconstruction, cover of severe corneal wound or tendon elongation in the eye (Niegowski et al., 2020; Ashena et al., 2021; Hedergott et al., 2021; Chen et al., 2022), odontology (Solakoğlu et al., 2022) and eardrum reconstruction (de Dorlodot et al., 2013; Sainsbury et al., 2022). Furthermore it has been employed to generate a variety of bioprotheses such as vascular grafts, patches for abdominal or vaginal wall reconstruction and heart valves (Rémi et al., 2010).

Beyond these current clinical options, decellularization has been revealed as a procedure to obtain less immunoreactive and highly biocompatible pericardial ECM for TE purposes. Here, we focus on the use of human decellularized pericardial ECM to generate supportive porous scaffold for administering bioactive components grown and purified from large-scale cell cultures such as mesenchymal stromal cells (MSC) and derived extracellular vesicles (EV). The specific requirements governing the processing of pericardium as starting material

and the regulatory oversight for their potential clinical application post MI are also highlighted.

Decellularized pericardial extracellular matrix as an implantable platform of therapeutic biologicals

Decellularization of native tissues consists in the elimination of the original cellular material offering an available source of biocompatible ECM allografts. Of note, its efficacy is mainly based on DNA and cell remnants removal, overlooking the preservation of structural, mechanical and biological properties of the native ECM. The resulting 3-D porous scaffolds are potentially capable of reducing the probability of exacerbated immunological response and Graft-Versus-Host Disease, and graft rejection once implanted. Commonly, cellular components removal can be achieved by the combination of physical, chemical and biological methods (Gilbert et al., 2006; Badylak et al., 2011; Crapo et al., 2011). In this sense, the optimal decellularization protocol does not only depend on the tissue itself (cellularity, density, lipid contents, and thickness), but also on the final application of the resulting ECM-based graft. To date, different approaches have been developed by using pericardium from bovine, porcine and human origins (reviewed in Inci et al., 2020; Grebenik et al., 2020). Interestingly, human decellularized pericardium has demonstrated a reduced reactive response and immunological rejection both *in vitro* and *in vivo* (Prat-Vidal and Bayes-Genis 2020). Moreover, it has been described the neoformation of blood vessels and nerves in cell-free pericardial scaffolds applied over infarcted tissue as well as significant improvement in cardiac function parameters and decrease in infarct size in pigs (Gálvez-Montón et al., 2015).

In addition, one of the main challenges in cardiac TE is to find an optimal biomaterial to serve as a scaffold for the delivery of bioactive components. Specifically, pore integrity and size, stiffness and elasticity are crucial to yield a scaffolding biomaterial with the optimal characteristics before being filled with the active ingredient (Loh and Choong 2013). The main goal is to facilitate the retention and local delivery with the aim of increasing the action of therapeutic biologicals, such as cells or EV. In this area of study, different pre-clinical studies based on the combination of pericardial ECM scaffolds and cells have been developed for the treatment of MI. Decellularized scaffolds, which are completely composed of ECM, constitute the natural environment of cells in the body, thus supporting basic cell functions including migration, proliferation, and differentiation (Inci et al., 2020). Importantly, the specific composition, 3-D structure and microenvironment of scaffold affect the survival and growth of the *in vitro* reseeded cells, together with a successful integration of the biomaterial into the host tissue (Grayson et al., 2009; Sarig and Machluf, 2011). In this

line, it has been reported that the preserved mechanical and structural properties of porous pericardial ECM following decellularization favors cell infiltration, retention and survival (Perea-Gil et al., 2018), thus making it an optimal scaffold for the manufacturing of reparative constructs (Prat-Vidal and Bayes-Genis 2020; Prat-Vidal et al., 2020). For instance, 3-D macroporous human pericardial scaffolds with well-defined architecture and interconnected pores enabled human Sca-1⁺ cardiac progenitor cells to migrate, survive, proliferate and differentiate at higher rates compared with collagen scaffolds (Rajabi-Zeleti et al., 2014). Moreover, histological examination of subcutaneous transplanted scaffolds after 1 month revealed low immunological response, enhanced angiogenesis and cardiac muscle repair in rats treated with pericardial scaffolds instead of grafts based in collagen (Rajabi-Zeleti et al., 2014). Allogeneic porcine induced pluripotent stem cells have also been delivered in decellularized pericardial ECM into pigs with experimentally induced MI, although this bioengineered construct was not effective in restoring cardiac function (Gálvez-Montón et al., 2017). It is also important to point out that the use of MSC in combination with pericardium, probably exerts a paracrine action of scaffold-retained cells while synthesizing new endogenous ECM which, in turn, increases the mobilization of resident precursor cells and ultimately the promotion of cardiac repair. MSC are self-renewing, *ex vivo* culture-expandable stem cell populations, with multipotent differentiation capacity and marked immune modulation potential, thus, considered immune privileged (Thompson et al., 2020). Indeed, in the pre-clinical setting, decellularized pericardial ECM has shown to be an optimal supportive scaffold for the delivery of cardiac adipose tissue-derived MSC to regenerate infarcted myocardium (Prat-Vidal et al., 2014; Gálvez-Montón et al., 2015; Gálvez-Montón et al., 2017; Perea-Gil et al., 2018). Cell-embedded pericardial ECM scaffolds limited the sequelae associated to MI, particularly reducing infarct size and improving cardiac function after implantation in post-infarcted pigs (Gálvez-Montón et al., 2017; Perea-Gil et al., 2018).

On the other hand, EV are the subject of growing research because they modulate efficient intercellular communication by transferring a variety of bioactive molecules such as proteins, lipids and non-coding nucleic acids (Yáñez-Mó et al., 2015). Thus, EV induce similar effects as the parental cells. For that, the use of EV for cardiac repair following acute MI has already begun to be explored pre-clinically. For example, the benefits of a newly-developed cardiac tissue engineering bioimplant combining EV derived from MSC with pericardial ECM has already been confirmed in infarcted pigs (Monguio-Tortajada et al., 2021). In particular, this therapeutic strategy was designed to use human decellularized pericardium refilled with EV obtained from porcine cardiac adipose tissue-derived MSC in order to guarantee local and sustained EV release over the infarcted area. As a result, the bioimplant was efficiently integrated into the post-infarcted myocardium after implantation, promoting

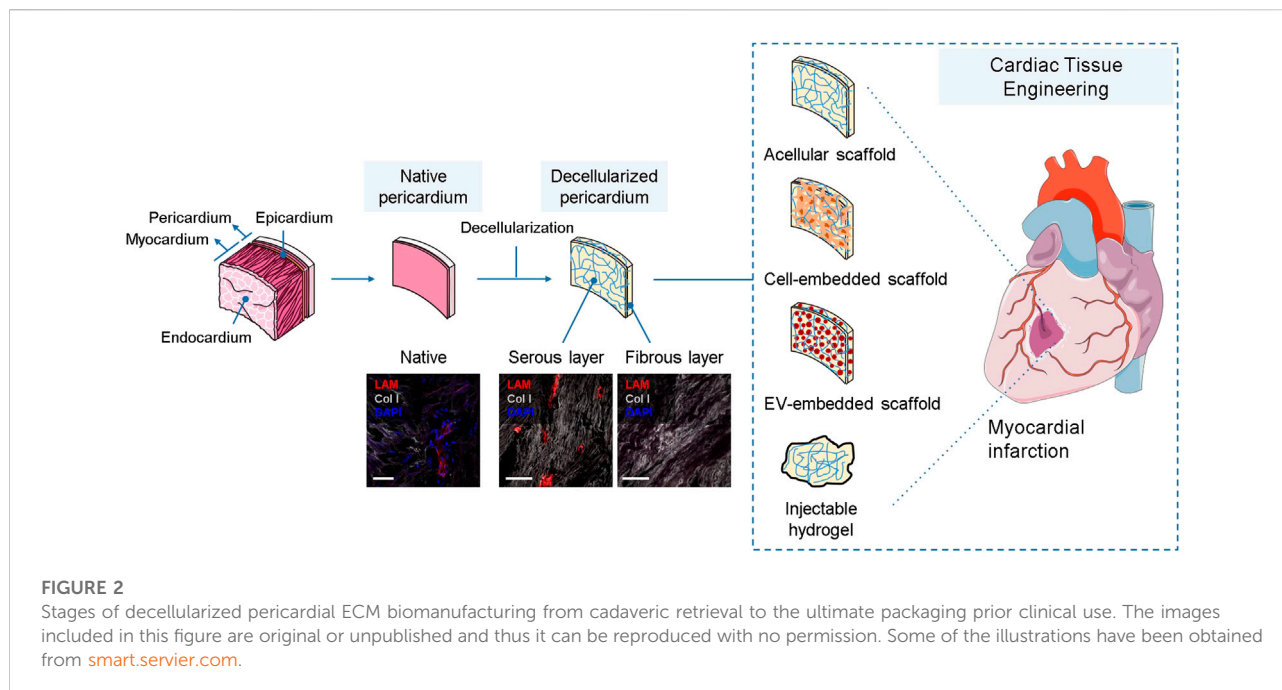
new vessel formation and decreasing tissue inflammation. EV were also detected into the infarcted myocardial area reducing tissue fibrosis and macrophage infiltration (Monguio-Tortajada et al., 2021). Indeed, the use of ECM comprising EV instead of the parental cells could have advantages, including the fact that EV are neither viable nor replicative components and its manipulation do not require as many precautions as with living cells. Also, due to EV size ranging from 50 to 200 nm in diameter, EV could reach more target sites with no thromboembolic complications once administered *in vivo* (Moll, 2022). Lastly, EV could be more powerful effectors over time because they constitute lipid bilayer-protected packages of multiple bioactive molecules.

Pericardial extracellular matrix as injectable hydrogels

Human decellularized pericardial ECM can also be processed into an injectable hydrogel and administered alone or in conjunction with active components to self-assemble *in situ* for cardiac repair. To date, although manufacturing standards are not well established for injectable types of ECM, ECM-derived hydrogels have been also studied due to their capability of being delivered in a minimally invasive manner *in vivo* (Hernández et al., 2020). For example, pericardium hydrogel injected in the left ventricular-free wall of a rat model, has been demonstrated to self-assemble shortly after injection. Moreover, it also provides a template for cell infiltration and neovascularization into damaged myocardium (Seif-Naraghi et al., 2010). Furthermore, the use of porcine decellularized pericardial hydrogel has not been associated with adverse inflammatory processes (Seif-Naraghi et al., 2012). In accordance, Seif-Naraghi et al. demonstrated that the sulfated glycosaminoglycan content of decellularized pericardial ECM hydrogel provides prolonged retention and delivery rates of basic fibroblast growth factor (bFGF). Also, in rodents, intramyocardial injection of bFGF embedded into a pericardial matrix enhanced neovascularization compared to an alternative delivery approach using collagen (Seif-Naraghi et al., 2012).

Essential requirements for pericardial extracellular matrix biomanufacturing

TE approaches still raise many questions regarding safety, quality, and efficacy according to the requirements of the European Tissue and Cells Directives (2004/23/EC and 2006/17/EC). At all stages of the human tissue manufacturing process, a quality management system must be applied, from identification of potential donors through processing and



storage to the final product for application to the patient. According to Good Tissue Practices (GTP), all the processes must be documented and validated to demonstrate that the quality and efficacy of the final product has not been compromised and avoid the potential risks such as microbial contamination or tissue damage (EUROGTPII Guide, 2018; Guide to the quality and safety of tissues and cells for human application, 2022). In particular, pericardium is obtained from cadaveric donors for transplantation purposes after the revision of social and medical history, physical examination, complete serological and microbiological testing, histopathological analysis, as well as any other information pertaining to risk factors for relevant communicable diseases (Figure 2). From the retrieval, the pericardium should be preserved in sterile containers until additional processing in a clean room environment. Processing steps include all operations involved in the preparation, manipulation, microbiological decontamination, preservation and packaging. The operations included in the preparation can comprise different activities such as thawing, washing, cutting, and soaking in decontamination solutions, sterilization, decellularization, lyophilization, and preservation before further product release. Importantly, all reagents used should be sterile, of the appropriate grade suitable for use in humans, conform to the national regulations and, when possible, should be approved for human use and CE (*Conformité Européenne*) marked. During processing and pre-packaging stages, effective and meaningful macroscopical and microbiological controls must be performed (Figure 2) (Guide to the quality and safety of tissues and cells for human application).

Recently, the use of human decellularized pericardial ECM, as a supportive platform to deliver therapeutic cells to the infarcted myocardium, has become a reality in clinical practice. In brief, we developed a novel double allogeneic pericardium-based investigational medicinal product (IMP), termed PeriCord, which combines MSC and human pericardium, to treat patients with a chronic myocardial scar (Prat-Vidal et al., 2020). The pericardial ECM is decellularized, lyophilized, sterilized and banked following GTP guidelines. The pericardial ECM is colonized with viable human allogeneic clinical-grade Wharton's jelly-derived MSC expanded and banked according to good manufacturing practices (GMP). The release criteria of the human decellularized pericardium included, among others, negative serological and microbiological testing of the tissue donors, no evidence of microbial growth, residual moisture <10%, and gamma irradiation (25–35 kGy). On the other hand, implanted clinical-grade Wharton's jelly-derived MSC meet all safety and quality standards regarding the number of cumulative population doublings, genomic stability, and sterility release criteria of the prior PeriCord manufacturing (Oliver-Vila et al., 2016). Remarkably, this IMP constitutes the first scalability and GTP/GMP-compliant biofabrication process that has reached clinical application in the context of MI, and is now being evaluated in the phase I PERISCOPE clinical trial (NCT03798353). Treated patients receive the PeriCord bioimplant, in the routinely surgical intervention, to cover the infarcted myocardial tissue. Preliminary safety data have already been reported after surgical implantation over a

myocardial area unsuitable for revascularization from a 63-year-old male patient (Prat-vidal et al., 2020). Full safety confirmation and potential benefit are expected from the ongoing PERISCOPE clinical trial.

Conclusion

Several pre-clinical studies have shown that implantation of natural ECM is a promising cardiac TE approach for post-MI treatment. In specific, the use of pericardial ECM scaffolds or its injectable version permits to increase the retention and beneficial effects of therapeutic biologics (e.g., MSC and derived EV) on the increase in myocardial revascularization and reduction of adverse inflammatory response. However, in order to guarantee its clinical translation, the biomanufacturing of these novel TE products must be faced from the tissue and cell banks according to the requirements of the European Tissue and Cells Directives. Moreover, the whole procedure must follow GTP and GMP.

Author contributions

CC-S, CP-V, and SR review data, wrote the manuscript and expressed final approval of the manuscript for publication. PL-C, OF, AB-G, LR-G, and AV critically revised the manuscript and expressed final approval of the manuscript for publication.

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Conflict of interest

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