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Ocular regenerative medicine using decellularized tissues

*Ajeesh Chandrasekharan [a], Erfan Yazdani [b], Aida Mahdian [c], Seyed AmirAbbas Shahidi Marnani [d], Shadi Askari [e]**

[a] Department of Biomaterials Science, Pusan National University, Miryang 50463, Republic of Korea
[b] Department of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
[c] Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[d] Faculty of Medical Sciences, University of Isfahan, Isfahan, Iran
[e] Department of Biomedical Engineering, Amirkabir University of Technology, Tehran, Iran

ABSTRACT

Decellularization is the process of eliminating the cellular compartment of living tissues chemically or physically, resulting in an acellular extracellular matrix (ECM) scaffold that can be employed for a variety of reasons. Decellularized matrices are useful for tissue engineering applications because they preserve the tissue-specific mechanical, biochemical, and structural microenvironments while facilitating cellular engraftment and activities in the matrix. A variety of tissues have been decellularized by a variety of mechanical, chemical, and enzyme-based techniques and used to create bio scaffolds for diverse cell types such as primary cells, progenitor cells, and stem cells. Various applications and approaches are used in ocular tissue engineering and regeneration. Repairing the damaged structure in the corneal epithelium or the retinal ganglion cells is one of them. Scaffolds of biocompatible, biodegradable, natural, or synthetic polymers may be used in such applications. Stem cells can also be used to replicate vital cells in order to maintain vision function. Decellularized matrices can be used to create scaffolds for ocular tissue engineering, artificial arteries, cell culture matrices, and transplantation carriers, among other things. To gain a better understanding of regenerative medicine, we'll look at different types of decellularized tissue matrices and how they've been used to create artificial organs and regenerate injured tissues.

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1. Introduction

To recover or maintain normal activity, tissue engineering tries to replace or regenerate human tissues or organs [1]. There are three basic components in tissue engineering: cells, signaling molecules, and scaffolds, all of which are interdependent. Pharmacological, biomechanical, and structural cues are provided by the scaffold and signaling molecules embedded into it to influence cell activity and tissue formation. Scaffolds may be made using a range of processes and materials, both natural and synthetic. Structure and mechanical qualities may be altered and managed to provide an ideal environment for a particular cell organization or cell type in synthetic scaffolds. When it comes to cell differentiation and proliferation, in particular, topography and matrix stiffness have a

* Corresponding author: Shadi Askari; E-mail: mapa4753@aut.ac.ir
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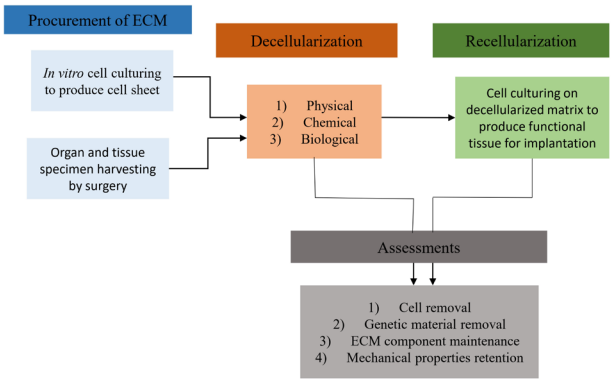

Fig. 1. Decellularization and Recellularization for biological tissues.

major impact. Stiff polymers like poly(lactic-co-glycolic acid) (PLGA) have been employed in bone and cartilage tissue engineering, whereas softer hydrogels have been used for soft tissues because of their variable mechanical characteristics and customizable composition [2-4]. When a matrix with similar stiffness to that of the actual tissue is used, the desired lineage can be promoted [5-7]. Cell regulation is often influenced by the scaffold's nanotopography. Additionally, nanotopography can influence the development of stem cells into specific cell lines such as muscle [8], bone [9, 10], and neuron [11-13] by influencing cell shape and gene expression. In this way, cells' behavior may be controlled by altering the scaffold's characteristics. It is possible to manage these qualities using electrospinning and 3D printing technologies, which optimize the materials and processing settings. A variety of tissues have been engineered with the use of electrospun constructions, consisting of bone [14-16], myocardium [17], and organized polymeric nanofibers [18, 19]. Using synthetic polymers or bioinks, 3D printing in scaffold design may also incorporate characteristics like scaffold architectural control and vasculature [19, 20]. For tissue engineering, these technologies have a lot of potentials since they can regulate the characteristics of the scaffolds and then influence cell activity [20, 21].

Since there are several difficulties in creating synthetic scaffolds that mimic the microenvironment of cells, there has been a high interest in using a native generated extracellular matrix (ECM). Decellularization is used to obtain this biological scaffold. It is the ultimate objective of decellularization to remove the ECM's original cell populations and genetic materials like DNA, while preserving its biomechanical, structural, and biochemical clues. Once the ECM has been decellularized, the patient's own cells can be incorporated into the tissue to create a customized product. Various tissues and organs, including livers, heart valves, tracheas, corneas, urine bladder, esophagus, kidneys, hearts, and blood vessels have been effectively reconstructed using decellularized ECM (dECM) [22-24].

Decellularization and recellularization are depicted in Fig. 1 as the major steps in the creation of designed tissues and organs. It is possible to eliminate DNA and cells from tissue while maintaining its structure and regulatory proteins using a variety of enzymatic, physical, and chemical approaches. Construct immune rejection to cells seeded on that can be prevented by removing cells and genetic material from the construct. These are the proposed criteria for determining whether or not the decellularized ECM has been effective: (1) fewer than 50 ng double-stranded DNA (dsDNA) per mg dry weight of ECM, (2) less than 200 bp DNA fragment length, and (3) no apparent nuclear material by 4′,6-diamidino-2-phenylindole (DAPI) staining [25]. In addition, the ECM's protein composition, particularly structural proteins like glycosaminoglycans (GAGs), fibronectin, and collagen as well as laminin, and growth factors, should be assessed. In addition, depending on the use, the mechanical parameters, such as tensile strength and elastic modulus, should match the original tissue. Additionally, the general effectiveness of the decellularization procedure is reviewed in this paper as well as several uses of decellularized ECM [26, 27].

Decellularized inner body membranes and their use in ocular tissue engineering (TE) are the focus of this study, which aims to give a comprehensive analysis and information of the current literature. Decellularization research on connective and epithelial tissue membranes are included in this review. Aside from a discussion of various decellularization procedures and the impact they have on membrane characteristics, the benefits and downsides are also examined for each type of decellularization.

2. Ocular tissue engineering challenges

The cornea, lens, retina, and optic nerve all work together to ensure that the eye functions properly. Vision is affected by one or more of these parts. Even while we've made great strides in the treatment of common eye disorders and defects, we still haven't found a cure for many of them. In many cases, transplantation is the sole option. After corneal blindness, keratoplasty is the only treatment that can restore eyesight [1]. A staggering 8 to 10 million people throughout the world are legally blind because of corneal disease and lack access to corneal tissue given by others. It's also possible that the number of people who accept corneas from other people could decline as a result of a growing number of refractive operations. Artificial and bioengineered corneas are gaining popularity as a solution to these issues. Corneal equivalents derived from three cell layers have been shown to have similar physical and physiological properties to those of human corneas in recent studies [2].

Retrovirus-transformed immortalised cell lines were used in these investigations, making them ineligible for use in transplantation. Stem cells have consequently become a key supply of tissues for cell-based therapies and corneal tissue engineering for ocular regeneration. Stem cells are capable of self-renewal, multilineage differentiation, and in vivo functional rebuilding of several tissues [3].

Since its inception in the early 1990s, TE has been touted as a potential treatment for severely damaged organs and tissues [28, 29]. To address inflammation, graft rejections, and donor shortages, following transplantation, the goal was to be able to replace and heal the disrupted tissue with an engineered one. While significant progress has been done, indicating that the TE idea is realistic, we have yet to overcome significant challenges in its implementation. Both cell-based and scaffold-based methods have been used by researchers in the field of TE to build artificial environments for cells before transplantation into the host. Over the past few decades, TE methods for ocular tissues have improved, however more therapeutically appropriate ocular tissue replacements are still needed [30]. There are several ways to use TE in ocular applications, as seen in Fig.2.

The barrier between the eye and its surroundings must be maintained by using TE techniques in the cornea. In terms of the three layers of the cornea (epithelium, stroma, and endothelium), replacing the stroma is arguably the most challenging. Stroma is the intermediate layer of cornea, which consists of a thick, translucent layer of collagen fibers as well as keratocytes, a kind of resident cell. 200 layers of collagen fiber approximately make up the stroma of cornea, which can make up to 90% of the cornea's overall thickness. Corneal transplantation is the sole surgical treatment for repairing corneas that have been injured or infected. In some cases, corneal tissue from a donor can be used to replace the entire cornea (penetrating keratoplasty) or just a portion of it (lamellar keratoplasty) [31]. Problems such as the danger of infection, the transplant rejection continues, and a lack of corneas despite some

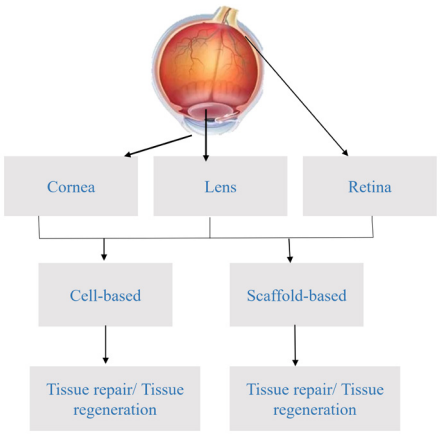

Fig. 2. Diagram of importance of tissue engineering: Cornea, Lens, and Retina.

success in the surgical procedure's implementation. An alternate path has been found in the effective development of the stroma of cornea in conjunction with the corneal endothelium and epithelia in multiple investigations, although long-term clinical applications and *in vivo* experiments are still missing. A range of TE applications based on cell and scaffold-based techniques can be applied to the corneal epithelium [32, 33]. Many encouraging results have been reported in studies involving the transplantation of limbal stem cells and mucosal epithelial cells [34, 35]. Amniotic membranes have also been employed in people for tissue transplants. There is still a need for long-term research in order to safely evaluate the advantages of these treatments [33, 36].

Despite the shortage in research focusing on TE treatments, there is a definite demand for less invasive methods of cataract removal than traditional surgery. Cataracts are currently treated by removing the lens surgically and substituting an artificial intraocular lens (IOL) for the natural one [37]. The posterior capsule opacification (PCO) necessitates a second procedure for the majority of patients who have cataract surgery. Because of the growth of lens epithelial cells on the capsule during cataract surgery, polychromatic cataract optics is a problem [38]. Alternatives are seldom being developed. Human retinal pigmented epithelium (RPE) cell line differentiation into lentoid and lens-like structures was described by Tsionis et al. [39] as one of the few TE techniques. It needs to be seen whether treatments based on this or other techniques will be available in the near future and whether TE is the future of lens-related clinical issues.

Most of the retinal TE studies have been done in animal models. Patients who received homologous transplants of RPE cells in the sub-retinal space had no improvement in their vision. Even while clinically substantial improvements in vision were achieved with autologous RPE cell transplantation, the little number of healthy cells that are able to be recovered from the patient is a major issue [13, 40, 41]. Polymers for retinal TE are a relatively recent idea, having evolved just in the last ten years or so. Thinner than 50 µm polymers that are biodegradable, porous, and having the right Young's modulus which is required for retinal transplantation, according to Trese and colleagues [42, 43]. The polymers poly (lactic-co-glycolic acid), poly(caprolactone) (PCL), poly(lactic acid), and poly(glucerol-sebacate), all meet this requirement. However, these and other polymers have only been tested in a few research for retinal TE applications with encouraging results. While conducting a month-long investigation, Thomson and co-authors [16] found that the blend of PLLA-PLGA polymer demonstrated good RPE cell adhesion, proliferation, and survival. However, the fundamental drawback of this examination was the reliance on cell lines rather than actual cells, that are well-known to behave differently. When it comes to regenerative medicine, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSs) are the preferred options. Cell-substrate based treatments must overcome a number of technological hurdles, regardless of the cell source [44].

Using decellularized tissue as a scaffold for tissue regeneration is an exciting prospect since it can give a more accurate representation of tissue structure and chemistry. Recent studies have shown that the use of decellularized extracellular matrix (ECM) as a scaffold material has been highly successful in the treatment of a wide range of tissues including the liver and cornea. Regenerative and developmental processes are known to be highly dependent on chemical cues, both insoluble and soluble, as well as structural signals. Acellular ECM has the benefit of having precise structural characteristics and chemical signals that enhance cell activities such as cell attachments, migrations, and signaling. This strategy is further supported by the retention of ECM components between species and the general tolerance of xenogeneic recipients. A cell delivery vehicle generated from natural retinal ECM may help RPCs survive and integrate better because of these facts [43].

Table 1.
Decellularization methods and their properties.

Method	Category	Agent	Properties	Ref.
Physical	Agitation	Mechanical stress	Cell death due to chemical exposure	[48]
	Freeze-thaw	Freeze-thaw cycle	Cell death due to intracellular water crystallization	[49]
	Supercritical fluid	Mainly CO_2	Cell death due to chemical exposure assistant	[50, 51]
	Pressure	Pressure	Cell death due to ECM biomechanical disruption	[52]
Chemical	Ionic detergents	SD SDS	Cell death due to cell membrane solubilizing	[53]
	Non-ionic detergents	Triton X-100 Triton X-200	Cell death due to disrupting lipid-lipid and lipid-protein connection in ECM	[54]
	Acids and bases	PAA and EDTA sodium hydroxide	Cytoplasmic component solubilizing	[55]
	Zwitterionic detergent	CHAPS SB-10 SB-16	Basement disruption due to ionic and non-ionic nature of solvents	[56]
	Alcohols	Ethanol	Cell lysis due to tissue dehydration	[51, 57]
	Hypotonic and hypertonic solutions	Sodium chloride solution	Osmotic shock induction cause minimum ECM disruption	[58]
Biological	Enzymes	Trypsin Pepsin Dispase DNAse RNAse	Ester/ peptide and nucleotide bond cleavage in cell membrane cause disruption	[59, 60]

3. Decellularized tissues preparation methods

A variety of decellularization methods have been used to create a variety of live organs over the years [45]. Cellular material is removed from the tissue while the ECM ultrastructure remains intact. The materials employed (reagent combinations) and the routes used to deliver the principal reagent, namely vascular, airway, or both, differ amongst decellularization procedures [46].

For the most part, tissue decellularization techniques may be broken

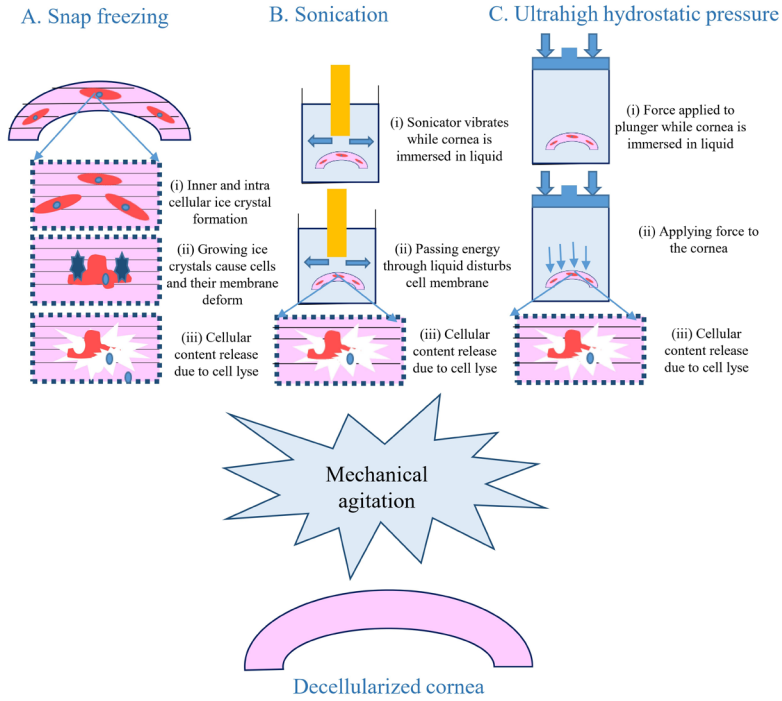

Fig. 3. Schematic of physical decellularization procedure.

down into three broad categories: physical (electroporation), biological (enzymes), and chemical (alkaline/acid) (Table 1). matrix thickness, tissue form, and cell density can all affect the quality of tissue decellularization. It is essential to decide which approach is best suited for a particular tissue because these features are varied in different tissues [47].

3.1. Physical methods

3.1.1. Freeze-Thaw

By repeatedly freezing and thawing tissues, the cells are lysed and destroyed, producing a decellularized matrix. Temperatures ranging from -80°C to 37°C are routinely used in freeze-thaw operations. Adjusting the temperature difference or the freeze-thaw number cycles can vary specific procedures. The decellularization of fibroblast cell sheets and the decellularization of canine lumbar spinal segments were two examples of freeze-thaw investigations. collagen content, GAG content, and mechanical strength were all comparable to the native specimen in both freeze-thaw experiments [61]. Even after treatment, the DNA in the fibroblast cell sheets remained at 88%. Results from this approach suggest an immunogenic response *in vivo* to the ECM scaffold that was created. Consequently, despite the fact that freeze-thaw techniques retain biomechanical qualities and biochemical components, they may cause immune rejection because of the inadequate genetic element removal [62] (Fig 3. A).

3.1.2. Agitation immersion and pressure

High hydrostatic pressure (HHP) is an emerging approach for disrupting cell membranes by applying more than 600 MPa pressures. HHP at 980 MPa for 10 minutes at 10 or 30°C decellularized swine corneas in one research [63]. On porcine blood arteries, an identical approach was used [22]. Although the high-pressure treatment killed the cells in both tissues, DNA fragments were left behind. Since HHP itself was unable to inhibit immune rejection in these trials, the wash solutions used in both investigations contained DNase I to break down fragments. A dextran, glucose polymer was added to the wash solution of cornea to minimize edema from the solution's submersion. One of the cornea's most important features, its transparency, and elastic moduli, is maintained by the addition of Glycerol [22] (Fig 3. B and C).

Protein quantity and structure can be altered by temperature fluctuations. Corneal decellularization at 10°C sustained higher levels of collagen and GAG than decellularization at 30°C did. It was found that the tissue structure was destroyed when ice formed at 10°C at HHP. As a result, the high pressure was found to denature ECM proteins, as evidenced by the deformation of collagen and elastin fibers in the decellularized blood arteries and the subsequent decrease in ultimate tensile strength by around 50%. The short duration of treatment and capacity to sterilize the tissue through the breakdown of viral and bacterial membranes make HHP therapy advantageous, but it necessitates a lengthy wash procedure and can affect the mechanical qualities and tissue's structural [22].

3.1.3. Supercritical Fluids

The temperature and pressure of supercritical fluids are so high that they can't be classified as either gas or liquid. A high permeability made it possible to eliminate these fluids without requiring any additional washing. Reduce hazardous ECM modifications by removing remaining cell fragments and decreasing ECM alterations [25]. A current trend in tissue decellularization is to employ supercritical carbon dioxide since its critical temperature is ideal for digesting ECM. Many research published recently claim that supercritical CO2 can remove porcine skin effectively and completely. When compared to standard detergent-based procedures, supercritical CO_2 not only decellularizes diverse tissues with superior preservation of ECM structure but is also employed to sterilize the dECM. Different supercritical CO2-based techniques used in the optic nerve, heart, and cornea resulted in cell elimination and preservation of ECM integrity [64, 65].

3.2. Chemical methods

3.2.1. Ionic and non-ionic detergent

Cell membrane and solubilizing DNA with ionic detergents weaken collagen's structural integrity by denaturing proteins. To remove GAGs and growth factors from the ECM, ionic detergents are extremely effective. SD, Triton X-200, and SDS detergents are ionic detergents that have been employed in decellularization processes. Sodium dodecyl sulfate SDS and SD in ovarian decellularization were studied by Alshaikh

et al [53]. They believe that SD preserves the ECM better than SDS, but that SDS contains less donor DNA. For this reason, it is necessary to use non-ionic detergents like Triton X-100 to eliminate any remaining SDS residue from the ECM before further washing with ionic detergents like SDS [53, 66, 67].

Detergents that are not ionic, such as Triton X-100, may effectively dissolve lipid-protein and lipid-lipid connections, while protein-protein interactions are more resistant to nonionic detergents. Decellularized tissue can be preserved in its ultrastructure and growth factors can be preserved. However, SDS is more successful in removing cell debris. When it comes to tissues where GAGs and other lipids are crucial, the Triton X-100 is not the best choice. For non-ionic detergents to be successful, the kind of tissue being decellularized must be taken into consideration [68].

3.2.2. Acids and Bases

Reversible alkaline swelling and peracetic acid are used in acid and base-containing treatments. When used for sterilization, peracetic acid is powerfully oxidizing corrosive. Peracetic acid has been used to decellularize tissues such as the urinary bladder and the small intestine submucosa (SIS) [26]. SIS was shown to be biocompatible after treatment. However, the cells remained. A large rise in elastic modulus and yield stress, notably in the longitudinal direction rather than the circumferential one, also affected the tissue's mechanical characteristics. As a consequence of changes in the alignment of collagen fibers, a stiffer ECM was created in the longitudinal direction in the urinary bladder matrix and submucosa treatment [69]. This suggests that peracetic acid therapy alters the tissue's function, which implies that it may not be ideal for tissues that require expansion and compliance. Tridecyl alcohol ethoxylate, a nonionic surfactant, was utilized alone and in combination with a calcium oxide alkaline solution in another investigation on the decellularization of bovine pericardium [70]. When used on its own, the tissue retained its original viscoelasticity and ultrastructure despite the absence of any cells. Adding the alkaline solution caused tissue swelling, which was then treated with ammonium sulfate to restore collagen's positive charge. A drop in GAG content and viscoelasticity occurred as a result of the swelling, although the elimination of cellular and genetic material was preserved. This compound was more dangerous than tridecyl alcohol ethoxylate alone, and it had no discernible effect in decreasing immune toxicity as a result [69, 70].

3.2.3. Zwitterionic Detergents

It is possible to use zwitterionic detergents as both ionic and non-ionic. Compared to non-ionic detergents, they have exhibited superior cell elimination and greater maintenance of the ECM ultrastructure. 3-[(3-cholamidopropyl) dimethylammonio)-1-propanesulfonate]-,SB-16, Tri (n-butyl) phosphate (TnBP), and Sulfobetaine-10 (SB-10) 3-[(3-cholamidopropyl) dimethylammonio)-1 propanesulfonate] (CHAPS) are among the Zwitterionic detergents. Tissue decellularization frequently employs the zwitterionic agent CHAPS. Protein-protein interactions are dissociated by TnBP, an organic solvent [47]. Cell elimination in tendon and ligament tissues was shown to be comparable between TnBP and SDS. Human saphenous vein decellularization using TnBP, deoxyribonuclease (DNase), and Triton X-100 was successful, according to Kuna et al [71].

3.2.4. Alcohols

Dehydration is a key factor in the determination of decellularization, since alcohols penetrate cells, reducing their DNA, disrupting cells, and replacing intracellular water. Lipids may be easily dissolved in alcohols like methanol and ethanol. Ethanol and methanol, because of their function in the fixation of tissue and deposition of proteins, may alter the tissue's ultrastructure. Acetone/ethanol decellularization resulted in stiffer tissue than SDS and Triton X-100, although the mechanical properties of the decellularized tissue were not adequately retained [25, 72].

3.2.5. Hypertonic and Hypotonic Solutions

Using solutions that are too hypotonic or too hypertonic might alter DNA and damage cells. Decellularization might be improved by using them in conjunction with other chemical compounds because they do not disrupt the composition of ECM [68, 73].

3.3. Biological methods

There have been several enzyme-enhanced decellularization techniques, similar to DNase I's usage in SD therapies to avoid DNA agglutination. Decellularization of both emphysematous and normal human lungs [74] and porcine heart valves [75] employed Triton X-100 and SD in conjunction with DNase to break down leftover DNA fragments and reduce possible immunogenicity *in vivo*. To treat the lungs, researcher used a perfusion and immersion method. Laminin, fibronectin, Collagens type I, and IV remained stable, although the GAG level decreased considerably following therapy [75]. Despite the preservation of myosin and actin, the amount of elastin is reduced. All of the lung's microstructure was preserved, including the alveolar septum. Three-day wash cycles were used to decellularized the heart valves, and the decellularized ECM was then digested using both DNase and RNase [74].

Trypsin, an enzyme typically employed in conjunction with EDTA, breaks cell-matrix adhesions, allowing cells to move freely. After 24 hours, all cells and genetic material had been removed from swine pulmonary valves [76]. Even at eight-hour treatment durations, the cell eradication was not complete. It was shown, however, that lengthier treatment times resulted in a reduction in collagen, GAGs, elastin, and mechanical strength. In addition, acid- and salt-soluble collagens were insufficiently maintained because of the characteristics of EDTA/ trypsin. There have been various methods that combine the aforementioned detergents since trypsin/EDTA therapy alone is ineffective. DNase, RNase, and Triton X-100 were used to decellularize pig heart valves in a research published in the journal PLOS One [77]. The nuclei of the cells were destroyed, but the elastin fibers remained intact. However, the heart valve's structural function may be negatively affected as a result of the deformation of collagen fibers. Trypsin was added in a five-cycle to the SD/DNase I regimen for the decellularization of pig trachea [78]. With the addition of 4 percent SD (4 hours at ambient temperature), 3 percent DNase I (3 hours of wash cycles between each new solution), and 1 percent trypsin (3 hours at 4°C) each cycle was completed. The elastic and collagen characteristics of the skin were not affected by the removal of cellular debris. In the trachea's cartilage, trypsin likely broke down chondronectin fibers, resulting in the removal of chondrocytes as the most important outcome of this decellularization therapy. This structure has been the target of several different therapies that have failed. Because of this, enzymatic therapies that may eliminate undesired genetic and cellular components from the ECM can improve chemical methods. ECM characteristics that are crucial for tissue regeneration must be maintained for these therapies to be effective [79, 80].

4. Decellularized tissues

The use of scaffolding materials for tissue regeneration is widely regarded as having immense promise. They have limited repair capacity due to the difficulties in overcoming immunogenicity, simulating in-vivo microenvironment, and performing mechanical or biochemical properties like native organs/tissues in spite of their widespread use and rapid

advancement of a number of tissue-engineered scaffolds, such as natural and synthetic polymer-based scaffolds. However, the development of dECM scaffolds, which replicate an ideal non-immune environment with native three-dimensional architectures and diverse bioactive components, presents an interesting option to overcome these difficulties. After seeding cells into dECM scaffolds with stem cells, the resulting cell-seeded construct is regarded as optimal for rebuilding functional organs/tissues [81].

4.1. Amniotic membrane (AM)

Over 60 years ago, ophthalmologists began using human AM transplants to treat eye diseases. There are several ophthalmic indications in which AM has been effectively utilized since 1995. When cryogenic preservation was developed in 1997, AM's popularity increased slightly [82]. Implanting AM can either be a long-term procedure or a short-term bandage or patch. A permanent graft of AM fills up tissue defects caused by illness or surgery by growing over or into the membrane, allowing host cells to grow into and over the membrane, which then become a permanent part of that tissue. The tissue may be an element of the ocular surface or a tissue plane beneath [83].

There is a Tenon replacement between both the sclera and conjunctiva (Tenon substitute or cover for a glaucoma drainage tube), a muscular sheath substitution among both the muscle and the conjunctiva, and under the scleral flap of a trabeculectomy. Keeping the ocular motility and filtration of aqueous fluid while preventing scarring is the primary objective of this treatment method. Sutures or fibrin glue can be used to sutureless attach AM to the host tissue in this mode, which allows it to be applied in single or multiple layers [84].

Also as a transient biological patch/ bandage, the primary purpose is to reduce inflammation in the host tissue in order to improve healing and minimize scarring from disease or surgical procedure. An AM dressing, patch, or dressing can be utilized to protect both healthy host tissue and the region of interest simultaneously, allowing the host epithelium to repair beneath. Recently, a medical device licensed by the US FDA, called ProKera®, has been used to distribute AM to cover the cornea without the need for sutures [85]. AM is normally removed or dissolved in the practitioner's office after the patient has been healed. Grafts and patches are sometimes used in conjunction, in which case the patch serves as a defensive cover to guarantee that the AM utilized as a graft is epithelialized [86].

It is possible to use a topical anesthetic and avoid suture-induced irritation with the aforementioned sutureless surgical techniques. More significantly, they make patient treatment easier by instantly transmitting the biological activities of AM, the foregoing medication, to the clinic or the patient's bedside. Because of this, disorders like chemical burns and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which require immediate treatment, might see a significant improvement in their prognoses. Once we learn more about the molecular mechanisms of AM, we may be able to develop novel therapies [87].

4.2. Lens capsule (LC)

As an epithelial basement membrane that completely covers the crystalline lens and separates the anterior and posterior eye segments, the human crystalline LC serves as a barrier. The anterior and posterior capsules of the LC are structurally separated in the equatorial region by collagen IV and laminin. The lens capsule eventually thickens as a result of the lens epithelial cells depositing ECM onto the capsule [88]. The capsule may roll up like a Descemet membrane when submerged in water and is translucent by nature, making it an appealing scaffold choice [89]. Cataract surgery, one of the most common operations worldwide, may provide anterior capsular material as a byproduct. In preliminary tests, corneal cells, including epithelial and endothelial cells, have been grown on the LC. The potential use of LC as an endothelial scaffold for the cornea was not investigated in our review [90].

4.3. Bruch's membrane (BrM)

To support the RPE on the retina's bottom part, the RPE is connected to a 2–5 nm thick protein matrix called BrM. Different ECM proteins may be found in the BrM's five separate layers, each with a unique structure. An elastic layer of elastin is sandwiched between BrM's outer and inner layers, forming the RPE's base lamina. In addition to supporting the RPE cell layer, BrM permits nutrients and waste products to enter and exit the retina. ECM proteins including collagen IV, laminin, fibronectin, and vitronectin are abundant in the BrM's deepest layers, where they bind to 1-integrins expressed on the basal surface of RPE cells [91].

Tongalp et al. explanted elderly Bruch's membrane obtained from five human cadaver eyes (donor ages, 69–84 years) and treated with Triton X-100 for decellularization and coated with a mixture of laminin (330 μg/mL), fibronectin (250 μg/mL), and vitronectin (33 μg/mL). On the surface, n = 15,000 viable human fetal and ARPE-19 cells were plated, and the RPE reattachment, apoptosis, and proliferation ratios were measured. For 17 days, cells were grown to determine the surface coverage. On aged BrM, the reattachment rates of fetal human RPE and ARPE-19 cells were comparable (41.5 1.7% and 42.9 2.7%, respectively, $P > 0.05$). With ECM protein coating, the reattachment ratio increased, but it reduced with detergent treatment. Combined washing and coating restored the reattachment ratio of fetal RPE cells but had no effect on ARPE-19 cells. The level of apoptosis was greatest in untreated BrM. Washing and cleaning in conjunction with ECM protein coating reduced fetal RPE cell apoptosis. 17 days after plating, only RPE cells grown on clean or clean and ECM-coated BrM exhibited significant surface coverage [92].

5. Application of decellularized tissues in cornea regeneration

In this respect, multiple groups have selected the pig cornea as a potential xenogeneic corneal matrix replacement to be decellularized. These research groups have applied several decellularization processes that were previously refined in tissues other than the cornea [93]. In an ideal world, a suitable protocol for decellularized cornea should be able to fulfill all 4 of the following standards criteria: (1) appropriate decellularization effectiveness, with removal of all cells and debris from the decellularized xenograft; (2) proper removal of all -gal epitopes; (3) appropriate potential of recellularization of the decellularized tissues utilizing host cells; and (4) appropriate decellularized corneas optical properties. Nevertheless, the effectiveness of the many procedures that have been reported to this point for decellularizing the cornea, which may or may not include the possibility of further recellularization of the acellular matrix, varies greatly. At the time that this article was being written, the process of recellularizing decellularized corneas using allogenic human keratocytes had not yet proven successful [94-96].

This is especially true for the cornea, where transparency is largely reliant on the architecture of the stromal matrix as well as the size, shape, structure, and density of the corneal cells, which are all critical factors [97]. Utilizing the method of direct summation of fields (DSF), Meek et al. [98] showed that risen refractive index mismatch, enhanced corneal thickness, and fibril disordering can all account for growth in light scattering in human corneas. They considered the cornea structure to be made completely of fiber of collagen and extrafibrillar matrix [99]. However, Mourant et al [97]. argue that the light dispersed at tiny angles would come from the cells themselves, the nuclei in the bigger

angles, and small organelles such as lysosomes and mitochondria in the larger angles. Aspects of the extracellular matrix and the corneal cells both play an important part in the human cornea's spectral transmittance function, which appears to be driven by light scattering procedure rather than absorption, the latter of which is only significant at extremely short wavelengths [100].

AM's anti-scarring effects are thought to be due in part to its anti-inflammatory properties, but there is also an indication that the AM stromal matrix suppresses the production of transforming growth factor-β (TGF-β) signaling in ocular tissue fibroblasts, therefore acting as a direct anti-scarring agent [99]. In a collagen gel contraction tissue culture model, human AM implanted into the stromal pocket of rabbit cornea inhibits myofibroblast development evoked by epithelial cells invading. Dendritic morphology and keratocan expression in murine [101], monkey [102], and human [103] keratocytes have been successfully maintained in culture using the AM stromal matrix. Therefore, inhibiting TGF-β signaling is not only vital in avoiding scar formation but also vital in preserving the normal keratocyte phenotype, which is critical for preventing scarring. Since then, He et al. in 2011 have shown that TGF-β promoter activity may be effectively suppressed by HC•HA isolated from AME and reconstituted from specified components, as previously reported. Both the anti-inflammatory and the anti-scarring effects may be mediated by HC•HA, according to these findings [98].

Using acellular corneal endothelium graft replacements for the first time was originally reported by Mehta and colleagues in 2017 [104]. Decellularized human Descemet's membrane was transferred into rabbit eyes in a method similar to Descemet membrane endothelial keratoplasty (DMEK), a process known as Descemet membrane transfer. A higher rate of migration in endothelial cells and a faster decrease in edema were observed in the allogeneic transplant group than in the control group that did not receive an allogeneic transplant. In Singapore, a human clinical trial is now being conducted to examine the efficacy of this approach. Following six months, the patient's best-corrected Snellen visual acuity improved from 6/18 to 6/7.5 after a 4 mm diameter decellularized descemet's membrane transplantation. The first clinical data were reported lately. Furthermore, the central density of corneal endothelial cells (CEC) was 889 cells/mm^2 while corneal thickness was lowered from 603 μm to 569 μm. For future research on acellular corneal endothelium graft alternatives to aid with CEC healing and edema decrease, this initial proof-of-concept study is a necessary first step [105].

Further research by Van den Bogerd et al. in 2018 investigated the LCsfeatures that make them a good scaffold for cornea engineering. They also evaluated the development properties of corneal endothelial cells in AM and human Descemet's membrane. Trypsin and EDTA were used to decellularized LCs, whereas cell scraping and thermolysin were used to decellularized HAM. To learn more about the morphology and phenotype of primary corneal endothelial cells, they were seeded on substrates and their immunohistochemistry characteristics were evaluated. According to the findings, cells grown on coated LCs had two times the surface area of focal adhesions as cells were grown on other membranes. The results also showed that the LC-cultured endothelial cells totally kept ion pumps, hexagonal shape, and tight connections. With these findings, it was concluded that the optical characteristics of LCs were adequate and that they were resistant to enzymatic degradation. After everything is said and done, LCs showed the required scaffold properties for tissue engineering and preserved cell phenotypes and might be used as a possible substrate for eye tissue engineering or as a blueprint for prospective scaffolds [106].

A transfection-free strategy was used by Fan et al. in 2011 to establish the first *in vitro* continuous line of human corneal endothelial cells (HCEs) and characterize cell-specific features [107]. HCE biocompatibility was also evaluated using decellularized AM, which is used to create tailored cornea replacements. Trypsin-EDTA and gentle scraping were used to extract DAM scaffolds. When grown under the right circumstances, HCEs were able to multiply and create single-layered cell sheets on the decellularized AM scaffold. TEM images also revealed connections between cells and the scaffold, indicating that the biomaterial is well-suited for ocular tissue engineering due to its high degree of biocompatibility. It has also been shown that tissue engineered-corneal endothelium (TE-CE) transplantation in a cat model can improve corneal function. To create the TE-CE, researchers used a previously developed monoclonal strain of HCEs and decellularized AM. The TE-CE group showed a steady reduction in thickness of cornea and no edema 104 days after lamellar keratoplasty surgery, but just decellularized AM transplantation induced significant corneal edema and an increase in graft thickness. New corneal endothelium was created by HCEs in the TE-CE transplanted eye, and these cells demonstrated intense intercellular junctions and similar morphology to normal cornea cells, although cell density was significantly lower than normal controls eye as determined by TEM, alizarin red staining, and SEM [107, 108].

6. Application of decellularized tissues in Retina regeneration

Epithelium, basement membrane, and stroma are three separate layers that make up the AM, which is the deepest layer of fetal membranes and includes an outermost spongy layer, middle fibroblast layer, and inner compact layer [109]. The AM is frequently stripped of its epithelial cells when it is employed as a TE substrate, such as in the retina. While the AM is very varied in thickness and other features, the mean thickness of denuded amniotic membrane is 9.8 (±4.3) μm. Concerns about disease transmission are exacerbated by the wide range of possible outcomes. Despite this, AM has been extensively employed in clinical practice for ocular surface repair treatments in patients with success rates ranging from 19% to 100% in patients [110] [111].

Two pigs with surgically induced choroidal neovascularization received AM as a BrM replacement in 2006 research. The migration of RPE cells into the d0amaged area was linked to the existence of an amniotic membrane in the affected area. Nevertheless, because the initial hemorrhage was followed by no further leakage, there was no way to say whether the AM helped or hurt choroidal neovascularization [112].

AM from pig fetuses increased proliferation more than RPE debridement, demonstrating that AM positively affects the epithelia. Debridement and AM transplantation resulted in the greatest rates of peripheral cell proliferation. *In vitro*, RPE cells separated from peripheral locations grew more rapidly than those from the center [113].

Researchers found that RPE cells expanding into debriding regions lost colour; those on the amniotic membrane, however, kept their pigmentation. However, this study found that the amniotic membrane was responsible for stimulating creation of new capillaries on its basal surface, which is remarkable because the amniotic membrane is typically regarded a blocker of new choroidal arteries [114]. Amniotic membrane orientation (epithelia solely present on the inner surface) and therapy were not well reported in the research. Amniotic membrane thickness should also be regulated to ensure consistency.

There are those who argue that only target tissue dECM can offer an accurate replica of the native ECM for TE because of the complexity of the ECM in tissues like the retina [115]. There has been an increase in the usage of dECM as a biomaterial, and it has been used to design diverse tissues, including via 3D printing [116].

Initially dECM from retina was described by Kundu et al. in 2015 [117]. Lyophilised powder was prepared from decellularized neural retina in adult cow eyes (age not specified) that was partly decomposed with pepsin before being utilized to make films. Sulfated GAG content was decreased by 45 percent, however 94% of DNA was eliminated and

80% of collagen and HA were maintained. Some essential growth factors, such as bFGF and NGF were also found to have been preserved, although their functionalities were not explored. A proliferation of adherent human RPCs in the dECM and the expression of ROM1, CRX, NRL, and Rhodopsin as well as other markers of photoreceptor differentiation, were both sustained by the dECM. To transfer RPCs into the subretinal cavity of the eye, Kundu et al. suggest using a hydrogel made from decellularized retinal ECM, although data from 2D culture do not support this theory because fibronectin was found to be superior. In respect of cell adhesion and proliferation, the dECM was less effective than fibronectin, even though both substrates seemed to induce retinal differentiation. While semiquantitative RT-PCR showed that ROM1 expression was much higher on dECM compared to fibronectin, this was not represented by the findings of the qRT-PCR study, and CRX and Rhodopsin expression seemed to be equivalent among dECM and fibronectin.

7. Advantageous and disadvantageous of decellularized tissues

Tissue engineering has made considerable use of DMs obtained from various organs and tissues, as mentioned in section 3. Details on each of DMs' benefits were provided here, including their low immunogenicity and bioactive compounds. Ease of organ replacement and biodegradability were also covered. Most DMs have porous properties as a result of eliminating cells and other antigen components from native tissues. To facilitate cell proliferation and adhesion, tissue engineering scaffolds need internal holes with a sufficient diameter that offer structural support for the cells metabolism and facilitate the nutrients exchanges [118].

A further benefit of these intricate 3D structures is that they were created during the evolution of life itself by self-assembly of ECM components following genetically directed growth programs, thereby providing the best possible environment for cells. The structural integrity of DMs is maintained at both the macro and micro scales, resulting in a tensile strength comparable to that of native tissue scaffolds [119]. ECM mechanics and ultrastructure have been shown to have a significant impact on cell migration, differentiation, and behavior as well as organ-specific cell fate determination, and organogenesis self-assembly [120].

Tissue-specific components can be found in decellularized materials from distinct tissues. Many other types of growth factors, such as fibroblast growth factor (FGF), fibronectin (FN), transforming growth factor (TGF), bone morphogenetic protein (BMP-2), vascular endothelial growth factor (VEGF), and laminin, are also found in most tissues [49, 121, 122].

Biomaterials can trigger the immune response to generate a more favorable micro-environment for tissue remodeling, but severe immune rejection and inflammation can reduce the repair impact and even worsen the defect state, even though it has been demonstrated that the immune response is necessary for tissue regeneration to some extent. Due to their limited immunogenicity and immunomodulatory properties, DMs have been demonstrated to induce very modest immune responses. Although allografts suffer from this disadvantage, DMs with relatively mild immune responses may be able to overcome it to a certain extent to produce an acceptable healing result. A better immunogenicity can be achieved with improved decellularization and post-processing procedures [123].

DMs might play a crucial part in the procedure of organ and tissue regeneration, since they could not only govern the healing procedure, but also disintegrate spontaneously when the repair is accomplished. DMs are generally constituted of natural biodegradable polysaccharides, glycoproteins, collagens, proteoglycans, etc. Thus, they might be disrupted with non-toxic degradation agents [124].

Organ transplants are in high demand, as is widely known. While the peri-operative survival rates for conventional allogeneic organ transplantation are outstanding, long-term transplant survival is still hampered by the possibility of graft rejection. Using appropriate materials to create artificial organs with low immunogenicity may help solve this issue. Rapid prototyping (which allows exact spatial control of polymers, growth factors, and cells) and guided self-assembly (achieved by genetic and/or chemical engineering) are two ways for fabricating artificial organs. Even yet, the development of a complicated organ with the desired in-vivo functionality and survivability is a challenging task. DMs offer numerous advantages, as seen in section 4, but there are still certain issues that need to be addressed, as outlined below. Also included in this section were the most recent fixes to each issue [125].

The kind of material, composition of the matrix, thickness, the density, and most importantly, the decellularization processes all affect the efficiency of decellularization. Because of advancements in decellularization techniques, the acellular matrix's antigenicity has been greatly lowered while its mechanical characteristics have been enhanced. Decellularization is still a difficult challenge to solve because of the lack of study on decellularization mechanisms and decellularization procedures, which restrict the types of DMs that may be used. If the collected or transplanted stem cells could not adhere to DMs with adequate mechanical qualities, their further proliferation and differentiation would be compromised. As a result, tissue and organ decellularization processes must be optimized in order to retain structural and functional integrity. These challenges might be solved by determining the best way for a particular type of tissue, refining current methods, or establishing new techniques [126].

As DMs decellularized, they lose part of their mechanical qualities as a result of the natural structures they interact with and the loss of proteins, collagen fibers, and cells among other things [127]. Cell attachment, cell phenotypic, and other factors are all affected by changes in the ECM's composition and rigidity. DMs with weak mechanical qualities may hinder the proliferation and differentiation of the cells that are collected or transplanted. These DMs may also increase cell-mediated stent compression, which will lead to a significant decrease in mechanical properties of the materials. Even more so, the use of these DMs in the repair of load-bearing sections would be limited. It has been an ongoing challenge to improve the mechanical characteristics of DMs [128].

Some bioactive compounds in DMs were lost or their three-dimensional structure was altered as a result of decellularization, which reduced DMs' ability to function to some extent. Bioactivities that help heal target tissues must thus be enhanced. Changes in the characteristics of DMs to reduce host reactions that impair tissue regeneration and introduction of other bioactive compounds to directly enhance tissue repair are the primary current options, as outlined in the following [129].

It is well established that the host's reaction to biomaterials is a crucial predictor of their tissue healing effects. Tissue healing might be harmed by severe host responses, particularly an immunological and inflammatory response. DMs bioactivities might enhance if host responses to tissue regeneration were suppressed. DMs' potential antigenicity has been shown to cause inflammation and rapid deterioration, hence several research have looked into ways of increasing bioactivity while decreasing the DMs' immunogenicity [130].

Adding additional bioactive substances to DMs may be divided into three categories: compensating for the loss of bioactive ECM components through decellularization, effectively altering them with active factors, such as related proteins and peptides, and functional materials [131].

Tissue regeneration rate should be matched to the optimal breakdown rate of biomaterials. However, DMs degrading too quickly at the implantation site remains a critical issue that must be addressed. Cao et al. in 2014 found that the rapid breakdown of decellularized scaffolds had a negative impact on the regeneration of cartilage. There were fewer

arteries and parenchymal cells after a period of observation, but only inflammatory cells and fibroblasts were detected, according to Zheng et al. in 2015. The breakdown rate of DMs has been researched using a variety of approaches, which may be grouped into two primary categories: crosslinking and coating. This methods can decrease the rate of degradation [132].

8. Conclusions and future perspective

Body membranes that have been decellularized are potential materials for use in tissue engineering applications. Decellularized versions of epithelial membranes and connective tissue membranes have been used in tissue engineering for the creation and regeneration of tissues including tendon, skin, cornea, bone, cartilage, ocular surface, uterine, periodontium, and cardiovascular. Although numerous research has been conducted to create ways for decellularization, decellularization agents must be improved for more efficient cell removal and fewer harmful effects on tissue structures and extracellular matrix (ECM). In addition, the development of decellularization agents that specifically target the elimination of major histocompatibility complex (MHC) and -gal antigens is vital, since these structures are one of the primary causes of tissue-organ rejections in allogeneic and xenogeneic tissue-organ transplants. In most cases, the mechanical properties of tissues decrease after decellularization; therefore, the combination of decellularized membranes with synthetic biomaterials could be used to improve the mechanical properties of decellularized membranes, as described in a number of previous studies.

In the next decades, it is anticipated that the tissues-organs that will be generated with progressively enhanced decellularization procedures would be the most accessible source of biocompatible replacement tissues-organs. Researchers in the disciplines of tissue engineering, biomaterials sciences, and regenerative medicine are anticipated to find this thorough study of decellularized inner body membranes and their applications in tissue engineering valuable.

With its many architectures, cell types, and tissues, the human eye is a good target for TE methods. The features of the eye and the lack of available treatments make this a very desirable tissue for TE. This is generally acknowledged throughout the scientific community, which is why big discoveries and advances in knowledge have occurred. Possibly the most successful tissue is the corneal epithelium. There is no reason why the other structures cannot be rebuilt or regenerated utilizing TE methods. The difficulty is in getting the scientists, engineers, and physicians to collaborate in order to meet the problems of today and provide the best possible care for our patients.

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