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Extracellular Matrix-Based Biomaterials and Their Influence Upon Cell Behavior

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Abstract

Biologic scaffold materials composed of allogeneic or xenogeneic extracellular matrix (ECM) are commonly used for the repair and remodeling of injured tissue. The clinical outcomes associated with implantation of ECM-based materials range from unacceptable to excellent. The variable clinical results are largely due to differences in the preparation of the material, including characteristics of the source tissue, the method and efficacy of decellularization, and post-decellularization processing steps. The mechanisms by which ECM scaffolds promote constructive tissue remodeling include mechanical support, degradation and release of bioactive molecules, recruitment and differentiation of endogenous stem/progenitor cells, and modulation of the immune response toward an anti-inflammatory phenotype. The methods of ECM preparation and the impact of these methods on the quality of the final product are described herein. Examples of favorable cellular responses of immune and stem cells associated with constructive tissue remodeling of ECM bioscaffolds are described.

Keywords

Biologic scaffold; host response; constructive remodeling; decellularization

1. Introduction: Bioscaffolds Derived from Extracellular Matrix

Biologic materials composed of mammalian extracellular matrix (ECM) have been effectively used for the repair and reconstruction of a variety of tissues, including skeletal muscle [68,162,229,255], esophagus [12,111,184,185], tendon [16,50,62,90,92], lower urinary tract

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5.Conflict of Interest

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[14,29,142,168,199], and heart [13,89,139,197,217,269], among others [52,87,137,138] in both preclinical animal studies and human clinical studies. These studies have largely shown constructive, functional tissue remodeling with the partial restoration of site appropriate tissue [9]. This deviation from the default tissue injury response of inflammation and scar tissue formation is consistently associated with modulation of the host innate and adaptive immune response [7,17,35,36,69] and the recruitment and differentiation of endogenous stem cells [2,23,69].

However, not all studies in which ECM-based materials have been used report this type of constructive healing response [236,260]. Alternative and less favorable outcomes include serous fluid accumulation at the implant site, rapid degradation of the material with associated mechanical failure in load bearing sites, or a lack of biomaterial degradation and an associated foreign body response [106,125,218,236,247,260]. These alternative outcomes have typically been associated with variations in manufacturing methods and/or source tissues. A partial list of commercially available ECM bioscaffolds is provided in Table 1 to show the variability of source materials and approved clinical indications. The present manuscript provides an overview of the effects of production methods upon the quality of and cellular response to ECM bioscaffolds.

2. Methods of Preparation

ECM bioscaffolds are typically prepared by the decellularization of mammalian tissue, either xenogeneic or allogeneic in origin, to produce a material consisting of the remaining native ECM, and the inherent signaling molecules therein. Though simple in principle, the manufacturing process of ECM biomaterials is actually quite complex and non-trivial. Considerations that must be taken into account include selection of the source tissue, method of decellularization, and inclusion of post-decellularization processing steps such as terminal sterilization or chemical crosslinking. The choices made at each step of manufacturing can markedly affect the physical and biochemical properties of the scaffold and the downstream cellular response and remodeling outcome. The characteristics of ECM bioscaffolds that can influence cell behavior are summarized in Figure 1 and described in detail below.

2.1. Tissue Source

2.1.1. Species—ECM bioscaffolds are prepared by decellularization and processing of source tissues harvested from humans (allogeneic) or other (xenogeneic) species. The constituent molecules of the ECM are highly conserved across mammalian species which is one of the reasons that devices manufactured from xenogeneic ECM do not elicit an adverse inflammatory response when implanted in humans. Basement membrane proteins, such as laminin and collagen IV, are some of the most highly evolutionarily conserved proteins [116,117,141] . High cross-species homology has been observed for other ECM components, including collagens [51,73], fibronectin [188], glycosaminoglycans (GAGs) [118,188] and growth factors [147]. Stated simply, bioactive ECM components are very similar across species; therefore similar cellular responses are elicited by allogeneic and xenogeneic bioscaffolds [131]. Importantly, the host immune response and downstream constructive remodeling are also similar between ECM-based bioscaffolds derived from different species [35,36].

Multiple studies have attempted to compare the cellular response to ECM scaffolds from xenogeneic and allogeneic sources [8,39,95,127,143,183,221,256]. However, a systematic comparison between bioscaffolds from different species is essentially impossible due to numerous confounding variables [131,256]. Commercially available biologic scaffolds can differ in the source tissue, tissue supplier, processing and sterilization methods, and packaging or storage conditions. The majority of the processing steps for commercial scaffolds are also proprietary which limits the ability to isolate specific factors that may affect the cellular response.

Allogeneic biological scaffolds are procured from cadaveric tissue and therefore allow limited control of variables that may affect the ECM properties, such as age or health status of the donor [127,131]. As discussed in detail below, the age of the source tissue, decellularization protocol, and post-decellularization processing can affect the cellular response to ECM bioscaffolds. Either innate species-related or age-related changes in the ECM between species often necessitate different decellularization or processing protocols for the same tissue type harvested from different species [127].

Commercially available human and porcine matrices have shown differences in the growth of fibroblasts in vitro [8], and the extent of cellular infiltration [39] and rate of remodeling [183] in vivo. VeDepo et al. compared species-specific effects of the same decellularization protocol on aortic valve tissue from human and ovine sources [256]. In this study, the same decellularization protocol was able to effectively remove cellular material from both species, despite almost triple the cell density in ovine leaflets compared to human. However, the same decellularization process induced different effects on the collagen crosslinking density, glycosaminoglycan content and mechanical properties of the ovine versus human tissue [256]. This study emphasizes the difficulty in isolating the species related differences in the cell response to ECM bioscaffolds.

2.1.2. Anatomic Site—The ECM consists of the structural and functional molecules secreted by the resident cells of an organ or tissue. Therefore the composition, structural and mechanical properties of the ECM vary widely for each tissue and organ [132,140,164,277]. As a result of these organ-specific differences in structure and composition, the isolation of ECM from diverse anatomic sites typically requires a tissue specific decellularization protocol. As described above, dissimilarities in the processing of ECM from different tissue anatomic locations makes direct comparison of ECM properties between tissues a challenging task. The native ECM of a tissue is the optimal substrate for survival, differentiation and function of the resident cells. Intuitively it would seem that exogenously implanted ECM bioscaffolds from the same tissue anatomic location (homologous) should provide advantages and improved outcomes compared to non-homologous ECM. However, in reality the impact of the anatomic site of ECM source tissue (homologous vs. heterologous) is often non-intuitive and not predictable.

Depending on the context or specific outcome measured, homologous ECM has been reported to be superior [57,132,140,164,219,276,293], similar [57,132,140,277] or even inferior [76] to heterologous ECM. For example, Keane et al. compared the response of esophageal stem cells to hydrogels derived from homologous esophageal mucosa ECM (eECM) and

heterologous small intestinal submucosa (SIS-ECM) and urinary bladder (UBM-ECM) [132]. Each tissue type had a distinct protein profile as indicated by gel chromatography. In vitro homologous eECM promoted migration of esophageal stem cells and formation of significantly more esophageal organoids than both heterologous ECM types. However, there was no difference in the size or number of proliferating cells within an individual organoid between eECM and UBM-ECM. In vivo, eECM and UBM-ECM promoted essentially identical remodeling of the esophageal mucosa [132]. This study suggested that homologous ECM does maintain some site-specific favorable properties of the native tissue, but these properties may contribute only minimally to the overall remodeling response.

The cell and host response to ECM derived from source tissue of different heterologous anatomic sites also varies. The biochemical composition of ECM hydrogels prepared from a wide range of heterologous tissue sources can promote different activation states of macrophages in vitro [71,166]. The mechanical properties of ECM prepared from different anatomic locations varies widely and can be misleading with respect to expected performance in different clinical applications. ECM bioscaffolds derived from dermis are stronger than UBM-ECM and SIS-ECM bioscaffolds. However, despite differences in pre-implantation strength, UBM-ECM [285] and SIS-ECM [149] have both been reported to promote equivalent strength of the implantation site as dermis ECM following tissue integration. Further, the ECM scaffolds derived from dermis showed little tissue incorporation and a poor remodeling outcome compared to UBM-ECM [285] and SIS-ECM [149].

2.1.3. Age of Source Animal—The age of the source tissue donor affects the mechanical properties and composition of the resulting ECM bioscaffold [153,154,215,231,246,271,272,275]. The ECM of fetal and neonatal tissues is enriched in glycosaminoglycans such as hyaluronic acid [152,215,245,267] and fibronectin [153] compared to adult ECM. Laminin [96], elastin [96,267], and growth factor [246] content is reduced with age. The collagen of young animals contains fewer crosslinks than that of adult ECM [155]; a factor that contributes to more rapid degradation of young ECM compared to the ECM of adults[246].

The changes that occur within the native ECM during aging have a direct effect on the in vitro and in vivo cellular response and remodeling outcome of decellularized ECM bioscaffolds prepared from these tissues. The first systematic examination of the effect of source animal age was performed by Tottey et al. in 2011 [246]. SIS-ECM bioscaffolds were produced from pigs that differed only in age (3, 12, 26, or >56 weeks old). Differences in the physical and compositional properties of the scaffolds were associated with a distinct cellular response in vitro. The ECM from 52 week old animals was significantly less chemotactic for perivascular stem cells than the ECM harvested from younger 12 week old animals [246]. ECM derived from old animals promoted an altered macrophage phenotype associated with reduced expression of both pro- and anti-inflammatory markers compared to ECM from younger animals in vitro [154]. In a pro-inflammatory environment, macrophages treated with ECM from 52 week old animals had significantly increased pro-inflammatory iNOS expression, decreased MHC-II expression, and decreased nitric oxide production compared to macrophages treated with ECM from 12 week old animals [154].

The host response and remodeling outcome to equivalent SIS-ECM scaffolds were evaluated in vivo following implantation in a rat model of abdominal wall repair [228]. ECM harvested from 3 and 12 week old pigs promoted the formation of more site appropriate skeletal muscle than ECM from older pigs. This constructive remodeling response to young ECM was associated with a predominately anti-inflammatory (M2-like) macrophage phenotype. Implanted scaffolds derived from 52 week old animals elicited limited cellular infiltrate that did not completely penetrate the thickness of the scaffold, and the macrophages that did infiltrate the matrix comprised a balance of pro-inflammatory (M1-like) and anti-inflammatory (M2-like) phenotypes. At 6 months post implantation of the 52 week old ECM, the site was characterized by deposition of a dense collagenous connective tissue with no evidence of innervation or new skeletal muscle formation, a stark contrast to the response to ECM from younger animals [228].

The impact of source animal age has also been demonstrated in the heart. ECM derived from the heart of fetal mice promoted increased adhesion and expansion of neonatal cardiomyocytes [231,275] and heart-derived progenitor cells [231] in vitro compared to adult mouse heart ECM. ECM from the hearts of neonatal mice promoted angiogenesis and increased endothelial cell activity compared to adult heart ECM both in vitro and in vivo [267]. In a mouse model of myocardial infarction, a single injection of neonatal heart ECM into the ventricle resulted in significantly improved dimensional and functional parameters at 6 weeks compared to adult heart ECM [267]. Neonatal ECM also significantly reduced fibrosis, ventricular stiffening and the chronic inflammatory response. The injection of adult mouse heart ECM did not show any significant improvement compared to saline control in any of the parameters evaluated [267].

2.2. Decellularization Efficiency

The ultimate goal of decellularization is the removal of all cellular components from the source tissue while preserving the complex structure and composition of the native ECM. In reality however, any process that disrupts and removes the cellular components of a tissue will alter the ECM ultrastructure and composition to some extent. Complete removal of all cellular remnants is not possible because of the intimate relationship between cell membranes and the surrounding matrix, the adhesive nature of the negatively charged nucleic acids, and the entrapment of cell debris within the structural matrix molecules. However, a balance between thorough removal of cells and maintenance of ECM integrity must be achieved to avoid a proinflammatory response when the ECM-based material is used as a biologic scaffold. The optimal decellularization method for each tissue depends on multiple variables including the tissue source, size, thickness, morphology, and cell and matrix density [274].

2.2.1. Adequate Removal of Cellular Material—Failure to adequately remove cellular material promotes an intense inflammatory response in the recipient that is associated with poor downstream tissue remodeling [134,150,210]. Keane et al. compared SIS-ECM produced by three different decellularization protocols and showed that more effective removal of DNA was associated with more favorable host tissue response in a rodent model of body wall repair [134]. However, DNA content is not the only determinant of the host

response to ECM scaffolds: mitochondria and cell membrane remnants also induced a pro-inflammatory response in a dose dependent manner in vivo [150]. There are likely many other yet to be identified quantifiable indicators of decellularization efficiency. The value in identifying such indicators is significant and additional work in the area is needed.

Although there are no standard criteria by which to determine adequate decellularization of a source tissue to produce an ECM biomaterial, Crapo et al. have suggested three quantitative criteria: 1) lack of visible nuclei in tissue sections stained with 4',6-diamino-phenylindole (DAPI) and hematoxylin and eosin, 2) less than 50ng of double-strand DNA per mg of dry weight ECM, and 3) fragment length of remnant DNA less than 200 base pairs [56]. These criteria are relatively stringent and may be too conservative for certain tissue types or applications [54]. In fact, many commercially available ECM scaffold materials fail to meet these criteria and are still associated with largely positive clinical outcomes [88,191].

2.2.2. Preservation of ECM Structure and Composition—The specific decellularization protocol can have dramatic effects on the mechanical and biological properties of the resulting scaffold [146,148,157,200]. A detailed description of the most commonly used decellularization agents and techniques and their effect on the ECM can be found in reviews specific to this topic [56,93,135]. In general, decellularization protocols consist of a combination of physical and chemical treatments.

Physical methods such as sonication, freezing/thawing, and direct application of pressure or force are commonly used to disrupt cell membranes and facilitate the release of cellular remnants from the scaffold. Physical methods can directly disrupt the structure of the ECM, but otherwise cause minimal damage to the composition and bioactivity of the material and therefore are safely incorporated into tissue processing protocols [135].

Chemical methods are generally more damaging to the ECM ultrastructure and molecular integrity than physical methods. However, use of these agents is often necessary to achieve adequate removal of cell debris. Each chemical agent has a unique mode of action in aiding cell removal and therefore has a different effect on the resulting ECM bioscaffold. Detrimental effects on the ECM can include removal of growth factors and GAGs, damage to collagen, and crosslinking of ECM proteins. Ionic detergents such as sodium dodecyl sulfate (SDS) and sodium deoxycholate (DOC) are effective decellularization agents but unavoidably alter critical ECM components such as basement membrane proteins and GAGs [74,200,232]. Non-ionic detergents such as CHAPS and zwitterionic detergents such as Triton-X 100 are less disruptive than SDS and DOC but also have detrimental effects upon composition and molecular integrity [74,171,201,232]. Exposure to solvents such as alcohols are typically included as a step in the decellularization of tissues with a high lipid content, including brain, pancreas and adipose [34,57,164].

The use of supercritical carbon dioxide as a decellularization agent is increasingly common and could represent an attractive approach which has relatively less disruptive effects[41,100,112,214,220,261,287]. The low viscosity and high transport rate characteristic of supercritical fluids enable short and simple decellularization protocols and the inert carbon dioxide causes minimal alteration of the ECM mechanical properties [41,112,135,214,261].

Not only can the combination of decellularization reagents change for each protocol, the concentration, duration, sequence of treatment, and technique for application are additional variables to consider. The complexity and duration of the overall decellularization protocol is often related to the geometric conservation desired in the ECM product (i.e. small pieces or slices vs. intact whole organ) [56]. In general, thin laminate tissues such as urinary bladder, small intestine, pericardium and amnion can be sufficiently decellularized with mechanical disruption followed by relatively mild detergents or acids [80,84,135,254]. Tissues that are more dense, such as dermis or myocardium, often require exposure to harsh enzymes (e.g. trypsin) and ionic detergents (e.g. DOC, SDS) for extended periods of time [126,200,222,276]. When access to intact vasculature is possible, removal of cellular material can be achieved by perfusion of the decellularization agent through the whole organ [28,75,196].

An often overlooked consequence of the use of such detergents is the necessity for thorough rinsing to remove residual detergent that can negatively impact the cellular response to the material [43,274]. A study by White et al. used time of flight secondary ion mass spectroscopy (ToF-SIMS) to detect residual detergents following decellularization of a UBM-ECM scaffold. Detergent fragments of DOC, SDS, and Triton X-100 were detected in the scaffolds despite extensive washing. Residual SDS in particular was associated with abnormal phenotype, poor viability and low confluence of cells in a dose dependent manner in this study [274] and in other studies [202,211,263].

2.3. Post-Decellularization Processing

2.3.1. Physical Form—The physical form of the ECM can dictate the relevant clinical applications of the ECM-based product, and can also directly impact the cellular response [72]. Immediately following the decellularization process, the ECM is typically in a hydrated state. Maintaining hydration of the ECM through the decellularization process better preserves the structural protein architecture (e.g., collagen) and promotes improved cellular infiltration and attachment compared to dehydrated/rehydrated scaffolds [85]. However the hydrated ECM is susceptible to continuous elution of soluble bioactive molecules such as cytokines and growth factors [200]. ECM-based bioscaffolds are therefore typically dehydrated by lyophilization to minimize the loss of soluble factors and improve stability (e.g., shelf life). Dehydration of the ECM also allows for further processing to change the physical form or configuration of the material.

Commonly used ECM-based medical devices such as those composed of SIS, UBM and dermis, are usually in a two-dimensional sheet configuration. Single-layer SIS-ECM and UBM-ECM sheets have a distinct “sided-ness” that can affect cellular behavior on the surface [33]. However single-layer SIS-ECM and UBM-ECM often lack the mechanical strength required for load-bearing applications such as body wall repair [90,247,253]. One method to increase the strength of the material is lamination of multiple sheets of ECM by vacuum pressing [80,83]. The multilaminate material can be specifically designed to minimize anisotropy of a single sheet (i.e. by altering the orientation of each layer), and to either maintain or eliminate the sidedness of the exposed layers [10]. Vacuum pressing can also be used to create 3-D shapes to fit an anatomical location such as the gastroesophageal junction or esophagus [10].

Single or multilayered sheet forms of the ECM have limitations of their clinical utility due to their fixed geometry and inability to be implanted by minimally invasive procedures. A powder or particulate form of the ECM can be obtained by comminution of the lyophilized sheet form of the material. The particle size, homogeneity and ultrastructure of the material depend on the source of the ECM and the method used to produce the powder [91]. The powder form retains the micro and ultrastructural characteristics of the parent ECM, but has greatly increased surface area available to interact with host cells [91]. Further, the powder configuration allows for manufacture of a compact 3-D scaffold [70,226], delivery by topical application [137,203,294], or injection of a suspension [48,208,235,239,280]. ECM powder suspensions have been successfully administered by injection, but the needle size required to accommodate the particle can be prohibitive for certain clinical applications, and a carrier such as glycerin is often required to increase the viscosity [10,280].

The discovery that the ECM could be manufactured into a liquid or gel form has greatly expanded its potential use in vitro and in vivo. The gel form can be more readily passed through a needle or catheter than a suspension of particles and can conform to the 3-D space upon injection [81,233]. The hydrogel form is produced first by solubilization of the ECM material into protein monomeric components (“pre-gel”) followed by spontaneous reformation of the intramolecular bonds into a hydrogel upon neutralization to physiologic conditions and exposure to body temperature (37°C) [31,81,209]. The most prevalent method of solubilization into the pre-gel form is enzymatic digestion of the powdered ECM with pepsin in a dilute acid solution [81,258], although other techniques have also been used [251]. Entropy-driven self-assembly into the hydrogel form occurs following neutralization of the pH and salts to physiologic conditions and raising the temperature to 37°C. Importantly, these properties allow delivery of the neutralized pre-gel as a viscous solution to an anatomic location where it will subsequently gel in situ. The gelation kinetics and mechanical properties of ECM hydrogels depend on multiple factors including tissue source, pre-gel concentration and neutralization conditions [128,145,151,251,276]. The formulation, characterization and cellular response to ECM hydrogels have been extensively reviewed elsewhere [209,240,264].

2.3.2. Chemical Crosslinking—Chemical crosslinking agents are frequently included in the processing of biologic scaffolds as a method to increase the mechanical strength and decrease the rate of degradation [158,190,268]. It should be noted that significant natural crosslinks exist within the structural molecules (such as collagen) of the native ECM. Chemically mediated crosslinking has also been investigated as a method to mask antigenic epitopes within the ECM after the decellularization process [55,181], although credible citations for the specific molecular basis and rationale of this approach cannot be found. In certain applications the use of chemical crosslinking may be justified and successfully implemented [26,46,123,158,213], but in general there are more negative consequences than positive consequences.

Glutaraldehyde is the most commonly described approach to crosslinking collagen-based materials, including ECM bioscaffolds. Glutaraldehyde increases the mechanical strength of scaffolds. However, glutaraldehyde is also associated various adverse effects including cellular toxicity and mineralization of the implanted material [4,159,216,234]. Alternative

crosslinking strategies have been investigated, primarily to mitigate cytotoxic effects. A wide range of crosslinking agents, including genipin [18,26,46,243,266,270], carbodiimide [17,44,186,253], hexamethylene diisocyanate (HMDI) [186,253], glyoxal [32], and vitamin B2 [123], have been considered and have generally shown improved biocompatibility compared to glutaraldehyde. The mechanism of action of the various crosslinking agents differs and can therefore confer specific effects on the surface characteristics and microstructure of the material. For example, carbodiimide crosslinked UBM-ECM scaffolds are associated with a dense, compact fiber network with small pore size [33]. Glutaraldehyde crosslinked ECM-based bioscaffolds produce thick bundles of collagen but maintain a similar pore size to that of non-crosslinked UBM-ECM [33].

Regardless of the agent used, the very nature of crosslinking changes the cellular response to the ECM scaffold. The process of ECM scaffold degradation generates bioactive cryptic peptides and releases embedded growth factors, cytokines and ECM-associated extracellular vesicles, termed matrix-bound nanovesicles (MBV), that contain protein, microRNA and lipid cargo [115]. These degradation products have been associated with chemoattraction of progenitor cells, recruitment and subsequent activation of macrophages toward a pro-remodeling phenotype, promotion of angiogenesis and antimicrobial activity. By definition, changing the degradation behavior of the ECM through crosslinking changes the release profile of these bioactive degradation products thereby eliciting a distinct, and often unfavorable, response. Finally, delaying or preventing ECM-based bioscaffold degradation results in a foreign body reaction [35,55,61,279].

The detrimental effects caused by chemical crosslinking of ECM bioscaffolds have been extensively studied, particularly in the context of soft-tissue repair. Multiple studies have evaluated commercially available scaffolds in a rat model of partial thickness abdominal wall repair [17,35,253]. The source tissue, bioscaffold configuration and processing methods that have been investigated vary widely. In all cases, chemical crosslinking of the ECM device has led to a poor remodeling outcome. Commercially available ECM products that are chemically crosslinked were invariably associated with the presence of multinucleate giant cells [253] and chronic foreign body response with associated fibrous encapsulation [35,253]. The same rat model has also been used to evaluate the effect of carbodiimide crosslinking upon scaffolds composed of SIS-ECM [254] and ACell MatriStem®, a commercially available UBM-ECM product [279]. Carbodiimide crosslinking was associated with minimal cellular infiltration into the scaffold [254], a predominately pro-inflammatory macrophage phenotype [279], and no evidence of degradation or remodeling of the scaffold [254].

Small animal [101,129,130,170,178], large animal [38,42,165] and human clinical studies [45] have all shown potential disadvantages of chemically crosslinked ECM scaffolds for ventral hernia repair. Implantation of non-crosslinked ECM scaffolds have been associated with significantly lower adhesion surface area and adhesion tenacity compared to crosslinked ECM scaffolds in both rat [130,178] and guinea pig [38] models of ventral hernia repair. Hernia repair in Yucatan minipigs showed greater cellular infiltration, ECM deposition and neovascularization for non-crosslinked scaffolds at 1 month post-surgery [42,165], consistent with improved early remodeling. No significant differences were observed in the strength of

the repair site at 1 month [42,165] or at 12 months [42] between crosslinked and non-crosslinked scaffolds, despite greater mechanical strength of crosslinked scaffolds at the time of implantation.

Pre-clinical studies have also found that Strattice™ (non-crosslinked porcine dermis ECM) is less susceptible to infection [178] and is better able to clear bacteria [101] in a deliberately contaminated surgical area compared to Permacol™ (crosslinked porcine dermis ECM). A retrospective review was conducted of patients who underwent abdominal wall hernia repair with Strattice™ and Permacol™ [45]. Non-crosslinked Strattice™ was associated with a significantly lower overall short-term complication rate, including significantly fewer occurrences of wound infection compared to Permacol™ [45]. A recently registered clinical trial will be the first randomized controlled study to evaluate the rate of recurrence and postoperative complications for Permacol™ versus Strattice™ in abdominal wall reconstruction [40].

2.3.3. Terminal Sterilization—The large majority of ECM-based biologic scaffolds are classified as a surgical mesh with the primary mechanism of action being “to provide reinforcement for soft tissue where weakness exists”, and therefore are regulated as a medical device by the Food and Drug Administration (FDA). According to the International Organization for Standardization (ISO) medical devices should be terminally sterilized to achieve a log10 reduction in virus sufficient to produce a safe product wherever possible, but aseptic processing can be used as an alternative (ISO 22442-1, ISO 13408-1)[119,120]. Though current FDA guidelines include case-by-case validation of sterilization of devices derived from animal tissue due to their complexity, terminal sterilization remains the standard for ECM bioscaffolds [249]. Allografts composed of human ECM are considered “human cells, tissues, and cellular and tissue-based product” (HCT/P) by the FDA and are therefore not required to be sterile. The industry standard for HCT/P includes the use of aseptic technique during harvesting and processing to prevent contamination [248].

Terminal sterilization is performed following the physical methods of tissue preparation, the decellularization process, and the occasional use of disinfection agents. Chemical disinfection agents (e.g., hydrogen peroxide or peracetic acid) can cause oxidation of ECM proteins and alter cross-linking patterns of collagen fibers [107], but the altered ECM can still support cell attachment [108,163]. Terminal sterilization processes can alter the ultrastructure, biologic activity and mechanical properties of an ECM bioscaffold which in turn can affect the cellular response to the material. Heat-based sterilization methods cannot be used for ECM bioscaffolds because the majority of ECM proteins are subject to irreversible denaturation at temperatures between 60 - 65°C [54]. The most commonly used methods of terminal sterilization for ECM bioscaffolds are ionizing radiation and ethylene oxide.

The effect of exposure to ionizing radiation, including electron beam and gamma irradiation, on ECM bioscaffolds has been investigated. Low doses of gamma irradiation (<15kGy) have been reported to increase the strength and stiffness of the scaffold [98], but higher doses decrease the mechanical properties in a dose dependent manner [60,98]. Gamma irradiation can induce structural [250] and biochemical [60,212] changes in the scaffold. Even very low doses of irradiation can affect collagen crosslinking [241] and the scission of collagen chains increases

with dose [19]. Gamma irradiation can also negatively impact cell attachment [163] and induce cell death due to peroxidation of residual lipids in the scaffold [175]. Dearth et al. found that increasing the dose of gamma and electron beam irradiation to 40kGy adversely affected the material properties and changed the degradation rate and cellular response to a porcine dermis ECM scaffold in vivo [60].

The reported effects of ethylene oxide (EtO) sterilization on ECM scaffolds are variable and depend on the parameters of each study. Exposure to EtO can have minimal effects on the mechanical properties [60,84,121] or can substantially increase the stiffness of the scaffold [204]. EtO sterilization did not affect the attachment or activity of fibroblasts [107] or endothelial cells [60] in vitro, but did inhibit cell attachment, proliferation, and viability of human umbilical cord Wharton's Jelly matrix cells compared to a non-sterilized scaffold [163]. Ethylene oxide reduces the DNA, total protein and growth factor content compared to other sterilization methods [60] and can render proteins inactive or undetectable by alkylation [63]. EtO treatment has the potential to leave behind harmful residues within the ECM that can cause an adverse host immune response and poor remodeling outcome [122], but has also been shown to successfully promote a constructive remodeling response in a rodent model of abdominal wall repair [60].

Sterilization by supercritical carbon dioxide is prevalent in food and pharmaceuticals [230], and is emerging as a promising technique for ECM bioscaffolds. Supercritical carbon dioxide sterilization has been shown to successfully inactivate a large panel of microorganisms [25]. Exposure of ECM scaffolds to supercritical carbon dioxide has shown minimal damage to the mechanical properties, tissue architecture and ECM content [20,25,104,287]. Bioscaffolds sterilized by this method support cell viability and proliferation in vitro [20,25,287]. Supercritical carbon dioxide has also recently been shown to successfully sterilize a hydrogel form of ECM while maintaining the ability of the solubilized ECM to form a gel and exert known effects upon macrophages and perivascular stem cells [273]. The host response to supercritical carbon dioxide sterilized ECM scaffolds has yet to be evaluated in vivo.

3. Favorable Cellular Response to ECM Bioscaffolds

As described in detail above, there are many factors that contribute to the overall quality of an ECM bioscaffold and each of these can affect the host response to the material. The seemingly endless variables involved in producing an ECM scaffold and the wide range of clinical applications make the definition of an "ideal" ECM bioscaffold impossible. However, when close attention is given to the variables known to affect the host response the chance for a favorable outcome can be maximized.

The term "constructive remodeling" has been used to describe the in vivo events that occur following implantation of a thoroughly decellularized, sterile ECM bioscaffold [9,12,36,68,162,255]. ConstructiVe remodeling is characterized by degradation and gradual replacement of the bioscaffold with site appropriate functional tissue. This type of in vivo response to an implanted biomaterial is in stark contrast to the default wound healing

response that is associated with a pro-inflammatory environment and the deposition of dense scar tissue.

As stated in the introduction, the remodeling outcomes following ECM bioscaffold implantation have not always been constructive [106,125,218,236,247,260]. A mild or intense inflammatory response and/or a serous fluid accumulation have occurred with associated scar tissue formation as occurs with the default wound healing response. Such results are commonly associated with ECM-based products that have significant cell remnants, residual chemicals from disinfection and decellularization processes, or the use of chemical crosslinking methods that alter structural and functional protein constituents and that inhibit or delay degradation of the scaffold [35,36,134,150,176].

Though the specific mechanisms by which ECM bioscaffolds promote a positive constructive tissue remodeling are not fully understood, the following processes are consistently associated with such outcomes: 1) degradation of the ECM bioscaffold to release bioactive signaling molecules [3,59,254], 2) modulation of the host immune response toward a pro-remodeling and regulatory type 2 phenotype [7,17,35,36,69], and 3) recruitment and differentiation of endogenous stem/progenitor cells [2,23,70]. The potential favorable response of immune cells and stem/progenitor cells to ECM bioscaffolds is described in detail below.

3.1. Immune Cells

Implantation of any material, including ECM scaffolds, is associated with the immediate adsorption of proteins to the surface. Competitive protein exchange results in a dynamic mixture of adsorbed proteins (Vroman effect)[105]. At early time points the composition is dominated by high concentration proteins that are eventually displaced by proteins with a higher affinity for the implanted material. Protein adsorption is followed by activation of the innate immune response, including dendritic cells, neutrophils and macrophages [11,49]. The adaptive immune system consisting of lymphocytes (B and T cells) may also be activated depending on the type of the biomaterial [78,174]. Both macrophages and T helper cells can assume diverse phenotypes that are characterized by their gene and protein expression profiles, and associated functions. In simplified terms, a proinflammatory phenotype of macrophages and T helper cells is associated with expression of cytotoxic signaling molecules, and a pro-healing and regulatory phenotype is associated with anti-inflammatory and regulatory signaling molecules [24,97,160,161,172,177]. ECM-based biomaterials that are devoid of cellular material, retain the ultrastructure and bioactive components of the native ECM, and that can be readily degraded by infiltrating host cells have been repeatedly shown to stimulate a strong pro-healing phenotype of both the adaptive and innate immune systems [7,17,35,36,39].

A seminal study by Allman et al. in 2001 showed that there is a robust host immune response to implanted ECM bioscaffolds with activation of T helper cells to a “Th2” phenotype. Implantation of porcine-derived ECM in a murine host elicited production of anti-inflammatory cytokines, including interleukin (IL)-4 and IL-10, and noncomplement fixing IgG1 antibody isotype. Both of these responses were consistent with recognition of the presence of the biomaterial, acceptance of the decellularized xenogeneic scaffold, and

lack of an adverse immune response. The constructive remodeling response to the scaffold was reported as T cell independent in this model although macrophage participation and macrophage phenotype were not examined[6]. Importantly, the strong Th2 response induced by ECM scaffolds was maintained following a secondary exposure to the scaffold [6] and therefore was not associated with an adverse sensitization phenomenon. The same group subsequently showed that ECM bioscaffold implantation did not cause generalized immune suppression, did not impair the antibody-mediated immune response to viral or bacterial infection, and did not impair the cell-mediated immune response to contact or xenogeneic skin graft rejection [7].

In 2009 Valentin et al. showed that ECM bioscaffolds induce a favorable host innate immune response, specifically the macrophage phenotype component of the innate response. This macrophage response was not only sufficient but was required for constructive remodeling of the scaffold [254]. Further, the early macrophage phenotypic profile induced by degradation of an ECM bioscaffold in vivo was predictive of downstream remodeling responses [35]. That is, increased infiltration of M2-like CD206+ macrophages and higher ratios of M2:M1 macrophages within the implantation site at 14 days were associated with more positive remodeling outcomes [35]. Macrophages exposed to the degradation products of ECM bioscaffolds can directly activate macrophages towards an anti-inflammatory “M2-like” (iNOS−/Fizz1+) phenotype [71,227]. The ECM-induced macrophage phenotype has been extensively characterized and is broadly associated with upregulation of anti-inflammatory genes and proteins [70,77,207], downregulation or suppression of pro-inflammatory genes and proteins [114,133], high antigen presenting capabilities [206] and expression of damage associated molecular patterns (DAMPs) [208]. Increased expression of DAMPS is hypothesized to contribute to a constructive wound healing response by amplifying endogenous wound-associated signaling pathways [208].

The macrophage phenotype induced by ECM bioscaffolds is complex and varies depending on the source and/or processing of the ECM [71,114,206]. The phenotype in response to ECM scaffolds is distinct from that induced by IFNγ + LPS (classically activated), IL-4 (alternatively activated), cellular xenogeneic scaffolds and synthetic scaffolds [114,208]. Importantly, the phenotype elicited by ECM-based bioscaffolds is different from that of tumor associated macrophages, another subset of M2 macrophages [278]. The activation of M2-like macrophages by ECM bioscaffolds is dependent on the presence of Th2 cells [207,278]. Although the exact mechanisms by which the ECM promotes a type 2-like immune response is only partially understood, it is known that degradation of the ECM and subsequent release of cryptic peptides, growth factors, MBV, and other bioactive molecules is required. Huleihel et al. showed that MBV alone can recapitulate the immunomodulatory properties of the parent ECM [113,115]. Whole UBM-ECM as well as isolated UBM-MBV can also activate microglia, the resident macrophages of the central nervous system, to an anti-inflammatory type 2 phenotype [76,169].

Recent studies have characterized the ECM-induced immune cells infiltrating within the bioscaffold and within the adjacent native tissue in detail with a multicolor flow cytometry panel and have shown robust populations of macrophages, dendritic cells, T cells and B cells [206-208]. The overall profile of infiltrating immune cells was significantly different between

ECM bioscaffolds prepared from different source tissues (bone, cardiac, liver, spleen and lung), but the general pattern was very similar [206]. ECM bioscaffolds elicited a higher proportion of T helper cells than cytotoxic T cells [206,207,265]. Regulatory T cells (Tregs) were also recruited to the site of implantation and were associated with increased levels of anti-inflammatory IL-10 cytokine secretion compared to autograft or saline [77,103,206,207].

Wang et al. used a humanized mouse model to characterize the temporal human immune response to xenogeneic and allogeneic decellularized myocardial ECM hydrogels. Although both decellularized scaffolds elicited a Th2 and M2-like macrophage phenotype, the quantity of cells and Th2 phenotype were more robust in response to the xenogeneic scaffold compared to the allogeneic scaffold. However, it is unknown if the amplified type 2 response was due to the xenogenecity of the bioscaffold or to differences in the source tissue, including older source age, greater collagen crosslinking and a more vigorous decellularization protocol associated with the allogeneic ECM [265].

3.2. Stem and Progenitor Cells

ECM bioscaffolds, or more specifically the products of ECM bioscaffold degradation, have been shown to be chemotactic for stem and progenitor cells in vitro and in vivo. [23,30,57,201]. Implantation of ECM bioscaffolds promotes recruitment of marrow-derived progenitor cells [15,288], cardiomyocyte progenitor cells [136,269,291], skeletal muscle interstitial stem cells [195], and perivascular stem cells to the site of implantation [70,229].

Perivascular stem cells (PVSC) are typically found surrounding microvessels and capillaries and can contribute to remodeling of acute skeletal muscle injury and contribute to the satellite cell pool if mobilized outside of their normal niche [64]. Implantation of an SIS-ECM bioscaffold in a volumetric skeletal muscle defect promoted mobilization of perivascular stem cells away from their normal perivascular niche to the site of the defect in both a rodent model and in human patients [70,229]. SIS-ECM implantation resulted in significantly more CD146+ PVSC both at the margin and the center of the remodeling ECM within the defect site and was associated with subsequent formation of functional vascularized and innervated striated functional muscle [70,229]. Although the specific mechanism directing stem cell recruitment is not known, cryptic peptides from the α subunit of collagen III recapitulate progenitor cell chemotaxis in vitro and site-directed accumulation in vivo [3].

The ability of ECM bioscaffolds to support stem cell differentiation or commitment towards a specific lineage is well established and has recently been reviewed in detail [1]. ECM derived from adipose [34,156,192,283,284], bone [102,242], central nervous system [18,57,66,164], cartilage [46,47,192,244,252,257,281], heart [65,67,79,82,86,127,198,231], kidney [28,37,187,205], liver [21,22,124,144,182,290], lung [53,58,94,180,223,225,292], salivary gland [224], skeletal muscle [65,110,194,195,229,262], tendon [99,189,282,286,289], among other tissues [5,109,167,173,179,193] have been studied in the context of stem cell differentiation. This concept is based upon the premise that the ECM of each tissue represents the secreted product of the cells that reside within that tissue, possesses tissue specific biologic signals, and is therefore the ideal substrate for supporting cell attachment, growth, and homeostatic differentiation [27,30,132]. These same concepts are part of the tissue organization field theory (TOFT) that, in part, supposes that the microenvironment created by the ECM facilitates either a normal or

neoplastic differentiation state [237,238]. ECM prepared in several different forms (whole organ, tissue slices, hydrogel, coating) have been investigated for their differentiation effects upon cells ranging from pluripotent embryonic stem cells to tissue specific progenitor cells [1]. ECM-induced stem cell differentiation in the context of the heart will briefly be described to highlight the potential of the ECM and bioscaffolds composed of ECM in directing cell fate.

In multiple contexts and culture systems, ECM derived from the myocardium has been shown to support cardiac cell differentiation or maturation. Gaetani et al. showed that 3D culture in a hydrogel from porcine ventricular ECM could support cardiogenic differentiation of human adult and fetal cardiac progenitor cells [86]. The myocardial matrix hydrogel promoted increased gene expression of cardiac markers (GATA-4 and MLC2v) and vascular marker (VEGFR2) in fetal cardiac progenitor cells. Expression of early cardiac markers (Nkx2.5 and MEF2c) and vascular markers (VEGFR2 and CD31) were also increased in adult cardiac progenitor cells after 4 days in culture within myocardial ECM hydrogel compared to a collagen type I hydrogel. The ECM hydrogel supported increased proliferation of the progenitor cells, and cells cultured within the myocardial matrix were better able to maintain viability in an environment of oxidative stress induced by hydrogen peroxide. This study demonstrated that a cardiac-specific hydrogel could enhance the cardiogenic commitment, proliferation and survival of human cardiac progenitor cells in 3D culture [86].

Though ECM bioscaffolds are most commonly used as a tool to help direct stem cell differentiation or commitment towards a specific lineage, one study instead looked at the ability of ECM to maintain an undifferentiated phenotype. De Waele et al. used decellularized mouse brain ECM sections as a 3D substrate for culture of rat neural stem cells [259]. In the presence of mitogenic stimuli (epidermal growth factor and human basic fibroblast growth factor), the majority of seeded neural stem cells retained their stemness and did not differentiate towards astrocytes or neurons after 7 weeks in culture [259].

4. Summary

Bioscaffolds composed of mammalian ECM have the potential to facilitate favorable remodeling processes in a wide range of clinical applications. The mechanisms by which ECM mediates constructive tissue remodeling include degradation and generation of bioactive molecules, recruitment and differentiation of endogenous stem and progenitor cells, and modulation of the immune response, among others. These positive outcomes are critically dependent upon the methods used to manufacture the ECM material. As described above, the source of the tissue, decellularization protocol and inclusion of additional processing steps affect the cellular response and remodeling outcome elicited by ECM bioscaffolds. Commercially available ECM products vary in their manufacturing methods and therefore can be associated with markedly different clinical outcomes.

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Abbreviations:

ECM	extracellular matrix
SIS	small intestinal submucosa
UBM	urinary bladder matrix
GAGs	glycosaminoglycans
SDS	sodium dodecyl sulfate
DOC	sodium deoxycholate
ToF-SIMS	time of flight secondary ion mass spectroscopy
HMDI	hexamethylene diisocyanate
MBV	matrix bound nanovesicles
FDA	United States Food and Drug Administration
ISO	International Organization for Standardization
HCT/P	Human Cell and Tissue Product
EtO	ethylene oxide
TOFT	tissue organization field theory
DAMP	damage associated molecular pattern
PVSC	perivascular stem cells

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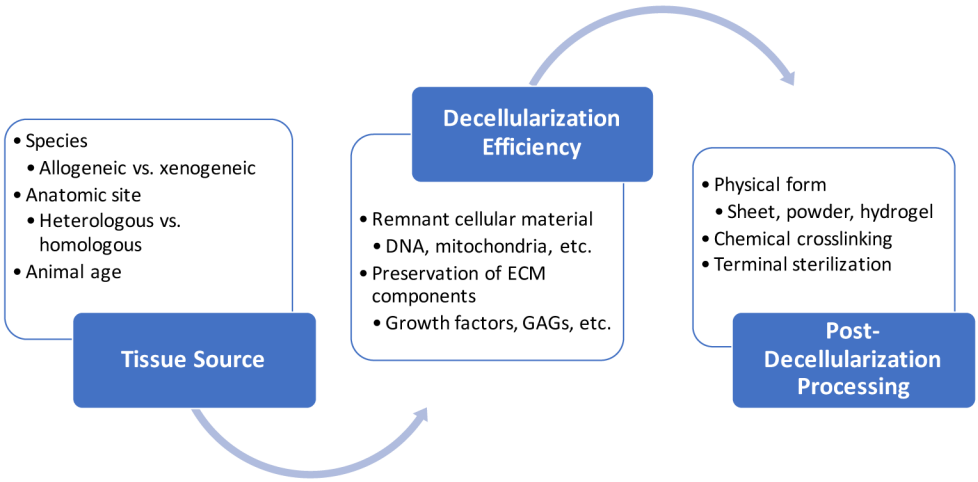

Figure 1.
Characteristics of ECM bioscaffolds that can influence cell behavior.

Table 1.

Source tissue, application focus and post-decellularization processing steps of common commercially available ECM bioscaffolds. (*VentriGel is in clinical trials, Glu: glutaraldehyde, HMDI: hexamethylene diisocyanate, Gamma: Gamma irradiation, E-beam: Electron beam irradiation)

Product	Manufacturer	Source Tissue	Application Focus	Form	Crosslinking Agent	Terminal Sterilization
AlloDerm RTM	BioHorizons	Human dermis	Soft tissue, dentistry	Dry	---	---
AlloMax	BD Bard	Human dermis	Soft tissue	Dry	---	Gamma
AlloPatch HD	ConMed	Human dermis	Tendon	Dry	---	---
Avalus	Medtronic	Bovine pericardium	Valve replacement	Hydrated	Glu	Liquid Chemical
Biodesign Hernia Graft	Cook Biotech	Porcine small intestine	Soft tissue	Dry	---	EtO
CardioCel	Admedus	Bovine pericardium	Cardiac tissue	Dry	Glu	Propylene Oxide
DermaSpan	Zimmer Biomet	Human dermis	Soft tissue, tendon	Dry	---	Gamma
FlexHD Pliable	Mentor	Human dermis	Breast	Hydrated	---	---
Fortiva	RTI Surgical	Porcine dermis	Soft tissue	Hydrated	---	Gamma
Freestyle	Medtronic	Porcine heart valve	Valve replacement	Hydrated	Glu	Liquid Chemical
Gentrix Surgical Matrix	Acell	Porcine urinary bladder	Soft tissue	6 Layer	---	E-beam
GraftJacket	Wright Medical	Human dermis	Soft tissue	Dry	---	---
Grafton DBM	Medtronic	Human bone	Bone	Powder	---	---
InteguPly	Aziyo Biologicals	Human dermis	Soft tissue, wound care	Dry	---	Gamma
Meso BioMatrix	DSM	Porcine mesothelium	Soft tissue	Dry	---	EtO
MicroMatrix	Acell	Porcine urinary bladder	Wound care	Powder	---	E-beam
Miroderm	Reprise Biomedical	Porcine liver	Soft tissue	Hydrated	---	E-beam
Oasis Ultra	Cook Biotech	Porcine small intestine	Wound care	3 Layer	---	EtO
Peri-Guard Repair Patch	Baxter	Bovine pericardium	Soft tissue	Hydrated	Glu	Liquid Chemical
Permacol	Medtronic	Porcine dermis	Soft tissue	Hydrated	HMDI	Gamma
ProLayer	Stryker	Human dermis	Soft tissue	Hydrated	---	E-beam
Strattice	LifeCell Corp.	Porcine dermis	Soft tissue	Hydrated	---	E-beam
Trifecta	Abbott	Bovine pericardium	Valve replacement	Hydrated	Glu	Liquid Chemical
TutoPatch	RTI Surgical	Bovine pericardium	Soft tissue	Dry	---	Gamma
Tutoplast Pericardium	Coloplast	Human pericardium	Soft tissue	Dry	---	Gamma
VentriGel*	Ventrix	Porcine ventricle	Cardiac tissue	Hydrogel	---	---
XenMatrix	BD Bard	Porcine dermis	Soft tissue	Hydrated	---	E-beam