HHS Public Access

Author manuscript

Biotechnol Adv. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

Biotechnol Adv. 2020 ; 42: 107421. doi:10.1016/j.biotechadv.2019.107421.

Extracellular matrix-derived biomaterials in engineering cell function

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Abstract

Extracellular matrix (ECM) derived components are emerging sources for the engineering of biomaterials that are capable of inducing desirable cell-specific responses. This review explores the use of biomaterials derived from naturally occurring ECM proteins and their derivatives in approaches that aim to regulate cell function. Biomaterials addressed are grouped into six categories: purified single ECM proteins, combinations of purified ECM proteins, cell-derived ECM, tissue-derived ECM, diseased and modified ECM, and ECM-polymer coupled biomaterials. Purified ECM proteins serve as a material coating for enhanced cell adhesion and biocompatibility. Cell-derived and tissue-derived ECM, generated by cell isolation and decellularization technologies, can capture the native state of the ECM environment and guide cell migration and alignment patterns as well as stem cell differentiation. We focus primarily on recent advances in the fields of soft tissue, cardiac, and dermal repair, and explore the utilization of ECM proteins as biomaterials to engineer cell responses.

Keywords

Extracellular Matrix; Acellular matrix; Decellularization; Scaffolds; Biomaterials; Cell therapy; Tissue engineering; Biopolymers; Repair

1. Introduction

1.1. Brief history and trends

In tissue, the ECM provides functionality, structural integrity, and suitable conditions for cell growth. The mechanical and biochemical cues within ECM can guide many cellular functions, such as cell migration and lineage commitment (Engler et al., 2006; Rho et al., 2006). More recent discoveries have strongly implicated the ECM in altering cellular behavior during disease progression (Walraven and Hinz, 2018), stem cell proliferation and differentiation (Reilly and Engler, 2010), and growth factor retention (Klingberg et al.,

2018). Therefore, native ECM proteins are considered as candidates for the development of biomaterials capable of inducing specific cellular behavior.

Beginning with purified proteins as biomaterial surface coatings, native ECM has evolved into more complex systems, such as cell-derived and whole-tissue-derived constructs. For example, the early commercial wound healing product Biobrane®, was a synthetic mesh conjugated with porcine collagen. It provided a temporary barrier between the wound bed and the air to protect the underlying cellular environment (Smith, 1995; Tavis et al., 1980). Somewhat more complex, the bilayer artificial skin product Integra® was introduced in the 1980s. It consisted of purified ECM components from cow and shark. The porous material allowed cells to migrate towards the open wound and begin regenerative processes (Burke et al., 1982). Harvested from cadaver skin, AlloDerm® became the first acellular skin substitute for the treatment of burn wounds and breast reconstruction (Wainwright, 1995). AlloDerm® largely retained the native dermal structure while possessing an enhanced regenerative potential. ECM proteins have also been explored for the creation of wound dressings and as carriers for delivering cells. Approved in 2001, Graftskin was one of the first “living” materials to employ bovine type I collagen to encapsulate viable fibroblasts to promote healing. In addition to providing material support, it preconditioned the wound bed with fibroblasts (Veves et al., 2001). Recently, special acellular materials, enriched in growth factors and derived from urinary bladder and placenta matrix, were used to improve wound healing (Choi et al., 2013; Meng et al., 2015; Rameshbabu et al., 2018). Of note, multiple clinical trials are currently investigating the efficacy of amniotic-membrane-derived material in wound healing (Moore et al., 2017)

Recent technological advances in decellularizing tissue and isolating cells allow the creation of functional complex biomaterials that take advantage of ECM proteins in their natural form. Bioabsorbable ECM polymers from decellularized tissue provide architecture and retain growth factors and protein modifications that are difficult to reproduce in non-native biomaterials. Moreover, *in vitro* cell-derived matrix (CDM) provides flexibility in manipulating matrix production and assembly via genetic or pharmacological modification without compromising its overall integrity. Finally, ECM constructs, when delivered *in situ*, provide a dynamic microenvironment capable of engineering specific cell responses. Figure 1 depicts representative scanning electron microscopy (SEM) images for the six categories of materials covered in this review.

1.2. Sources for isolating ECM

Various organs and tissues are regarded as suitable reservoirs for several ECM proteins. Table 1 lists the commonly used tissue sources of ECM proteins. Typically, tissues are isolated and processed through mechanical disruption, enzymatic digestion, chromatography, and precipitation. Though these traditional purification methods are effective, they lack the flexibility afforded by adding specific modifications to proteins. Recombinant technology has enabled the rapid production of ECM proteins *in vitro* with the ability to tune, modify, and manipulate the expressed protein (Even-Ram and Artym, 2011; Trabbic-carlson et al., 2004). Bacterial and eukaryotic cell lines have been used as carriers for producing ECM proteins such as recombinant fibronectin fragments (Amaral et al., 2013;

Neubauer et al., 2016; Yun et al., 2015), various types of collagen (Bulleid et al., 2000; Que et al., 2018; Stoichevska et al., 2016), human tropoelastin (Martin et al., 1995; Wang et al., 2016), and laminins (Kortesmaa et al., 2000; Rodin et al., 2010). Such *in vitro* expression systems are highly reproducible and inexpensive. However, species-specific post-translational modifications have been shown to induce undesirable host responses *in vivo*, including allergic reactions to gelatin-stabilized vaccines (Olsen et al., 2003).

To create biomaterials for tissue specific regeneration, ECM can be extracted from organs and tissues using decellularization and isolation techniques. However, allogenic and xenogeneic sources exhibit limited long-term efficacy due to the innate and adaptive immune response. Skin substitute products, like TransCyte® and OrCel®, delivered allogeneic fibroblasts to the wound site and exhibited regenerative capacity in short-term studies. Nevertheless, an unfavorable host response and the products' inability to vascularize the implant resulted in massive cell death and limit the long-term efficacy of these constructs (Varkey et al., 2015).

1.3. Advantages and disadvantages compared to synthetic materials

Native ECM-derived biomaterials, unlike synthetic materials, constitute a dynamic environment that can be processed, remodeled, and replaced during cell therapy (Gattazzo et al., 2014). Synthetic materials such as polyethylene meshes and silicone devices can trigger a foreign body response when implanted, leading to the generation of a fibrotic capsule that isolates the material from the surrounding tissue (Morais et al., 2010). ECM-derived biopolymers can mitigate the foreign body response by presenting ECM molecules at the interface between material and tissue. ECM-derived materials can evoke an innate immune response to replace the implanted matrices with new ECM for host integration. However, materials using allogenic and xenogeneic sources can evoke an adaptive immune response and cytokine release that might shorten the lifespan of the materials. Badylak and Gilbert (2008), Lopresti and Brown (2015), and Morris et al. (2017) have extensively discussed immune response to biomaterials.

As alluded to in section 1.1., native ECM constructs preserve the overall architecture of the matrix. The use of proper enzymatic and non-enzymatic agents, as well as a gentle detergent such as Triton X-100, can retain ECM proteins and matrix-bound components, such as growth factors, to a great extent. Reviews from the Badylak group (Crapo et al., 2011; Gilbert et al., 2006) has comprehensively addressed the effects of the decellularization process on the mechanical and biochemical integrity of ECM. Decellularized constructs have been shown to provide structural support, adhesion sites for cell attachment, and growth factors for cell proliferation (Kim et al., 2017; Wilson et al., 2016). In general, these materials are considered to be more desirable than ECM-modified synthetic constructs fabricated from electrospinning and electrospraying. This is due to the inability of these two techniques to create the multiplex assembly needed to resemble the native ECM. In terms of engineering specific cellular responses, polymers can be modified via functional group chemistry to decorate them with ECM proteins that can increase biorecognition (Benoit et al., 2007; Chu et al., 2018b; Ghosh et al., 2006). Nevertheless, native ECM constructs are considered superior to polymers in supporting tissue regeneration.

Tissues exhibit different physiological stiffnesses in order to provide the optimal environment for cell growth and function (Discher et al., 2009). Such variation cannot be precisely reproduced in native ECM materials due to limitations in processability. Partial modification can be achieved by chemical crosslinking reactions via glutaraldehyde and EDC/NHS chemistry to increase ECM stiffness. However, such changes were shown to be associated with decreased porosity and degradation rate, making the material suboptimal for cell infiltration and host integration (Ye et al., 2010). On the other hand, synthetic polymers, such as polyethylene glycol (PEG), can be easily made into controlled thickness and porosity. As a result, hybrid materials that augment ECM proteins with stronger synthetic polymers were invented to control porosity and the rate of degradation by modifying the polymer backbone while still retaining biocompatibility through surface modification or a coating (Chen et al., 2018; Goyal et al., 2017; Noh et al., 2016).

2. Naturally derived biomaterials and their applications

2.1. Purified single ECM protein biomaterials

Type I collagen is the most abundant structural protein in soft tissue and one of the earliest ECM components to be identified and isolated. It provides cells with a three-dimensional environment that supports cell growth and influences morphology and function. During tissue repair, collagen was shown to promote cell adhesion and migration by engaging cell surface receptors such as integrin β_1 subunit (Hynes, 1992), glycoprotein VI (Smethurst et al., 2007), non-specific receptors, and integrin-like receptors (Gullberg et al., 1989). The triple helix structure of collagen offered several favorable characteristics for engineering cellular functions, including thermal stability and mechanical strength (Shoulders and Raines, 2010).

Based on the properties mentioned above, type I collagen is the most popular native material for delivering cells or inducing specific cellular behavior for soft tissue regeneration. Collagen can self-assemble under physiological conditions, absorb onto surfaces through nonspecific interactions (Wallace and Rosenblatt, 2003), and be electrospun into biomaterials (Joshi et al., 2018; Rho et al., 2006). Type I collagen has been used in cell culture as a substrate to study and promote angiogenesis (Cross et al., 2010; Luwang et al., 2018; Ryan et al., 2019), as a wound dressing to treat burn wounds (Oryan et al., 2018), as a vehicle to encapsulate stem cells to induce dermal regeneration (Altman et al., 2008), and as a scaffold to generate a skin substitute for grafting (Trottier et al., 2008). Through integrin signaling and growth factor sensing at its interface with cells, a collagen matrix has been shown to maintain mesenchymal stem cells (MSCs) stemness (Engler et al., 2006; Mauney et al., 2005) or direct stem cells towards specific lineages for tissue regeneration (Farrell et al., 2006; Grier et al., 2018; Laiva et al., 2018). The compatibility between collagen matrices and MSCs enabled a collagen scaffold to serve as a cell delivery vehicle for diabetic wounds to promote repair via improved angiogenesis (Holst et al., 2013). Chattopadhyay & Raines (2014) have generated a comprehensive list of collagen-based biomaterial and commercial products.

Fibronectin promotes cell adhesion and controls cellular functions via peptide domains, including various binding sites for cell surface molecules and other biological molecules

such as heparin, fibrin, collagen, and growth factors (Klingberg et al., 2018; Pankov, 2002). The soluble form of fibronectin mainly circulates in plasma. The application of plasma fibronectin is limited to direct application of an aqueous solution, passive absorption, and covalent linkage to the surface of a biomaterial to promote bio-recognition and biocompatibility (MacDonald et al., 2002; Macdonald et al., 1998; Okada et al., 1985; Qiu et al., 2007). These methods lack proper spatial control over deposition. Electrospraying was developed to deposit soluble fibronectin onto the surface of a material with controlled density, thickness, and pore size for optimal cell migration and adhesion (Martyn et al., 2011). Another difficulty in developing fibronectin-based biomaterials is that soluble fibronectin in an aqueous solution cannot be utilized directly to constitute a biomaterial. Thus, recent work has focused on engineering biomaterials for cell therapy from lyophilized powder and precipitated plasma fibronectin. By using a rotary jet spinning technique, human fibronectin was made into nanofibers and assembled into meshes that could be used to improve dermal wound healing (Chantre et al., 2018). By using concentrated fibronectin solution, a large fibronectin mesh was produced after mixing with 0.25 M hydrochloric acid and 2% calcium chloride solution, or from passing through an ultrafiltration cell under constant stirring (Ahmed et al., 2003). Such fabrication methods retain the ability of fibronectin to promote cell adhesion. More importantly, these approaches allow for the production of engineered fibronectin-based three-dimensional constructs.

Other ECM proteins such as (tropo)elastin and laminin present in basement membranes are used in strategies to elicit desired phenotypes for cell therapy. Specifically, different peptide sequences in elastin are employed to generate scaffolding for cell regeneration therapy. These elastin-like polypeptides self-assemble into a gelatinous material above their transition temperature due to the unique thermo-responsive properties. Alternatively, they can be crosslinked by enzymatic reactions. Previously, such aggregates were applied in cartilage regeneration (Betre et al., 2002; McHale et al., 2005) and were also used to encapsulate adipose-derived stem cells (ASCs) for full thickness dermal wound healing (Choi et al., 2016). The effect of an elastin construct on maintaining stemness was also interrogated; the author found that the elasticity and tensegrity of the construct were necessary to provide key mechanical cues for maintaining and expanding hematopoietic stem cells (Holst et al., 2011). A novel manufacturing process called HeaTro, which utilizes tropoelastin as the sole ingredient to manufacture scaffold in different shapes and forms, was invented in the lab of Dr. Anthony Weiss. Mouse and pig full-thickness wound models were used to evaluate the *in vivo* performance of the HeaTro product. When compared to the Integra Dermal Regeneration Template, increased vascularization was observed in the proximity of an implanted HeaTro-generated scaffold, pointing to the great therapeutic potential of elastin-based products in wound healing (Mithieux et al., 2018).

Laminin 111, a major epithelial ECM component, has been used as a component of Matrigel® to provide a basement membrane-like scaffold. In addition, it has been used in electrospinning to construct fibrous meshes on a charged surface with tunable pore size and fiber diameter. The engineered meshes could maintain ASCs attachment and viability *in vitro,* and could induce them to develop neurite-like structure (Neal et al., 2009). Laminin 111 has also been shown to participate in other biological processes, including angiogenesis and neural differentiation (Li and Chau, 2010; Neal et al., 2009; Nicosia et al., 1994).

However, in recent years, more effort has been dedicated towards investigating the remainder of the 16 known laminin isoforms and their subunits. Laminin 511 was found to maintain the pluripotency of mouse embryonic stem cells through β_1 integrins, while laminin 411, 332, and 111 caused either rapid differentiation or cell death (Domogatskaya et al., 2008). By ablating laminin $\alpha 1$ chains in a murine skeletal muscle injury model, it was found that it plays a critical role in maintaining and activating satellite cells (Rayagiri et al., 2018). For further discussion on this topic, please refer to the book chapter on laminin isoforms written by Dr. Anna Domogtskaya and Dr. Sergey Rodin (Domogatskaya and Rodin, 2018).

ECM proteins like collagen, fibronectin, elastin, and laminin are readily accessible through isolation or transgenic expression. The availability of pure ECM proteins allows researchers to investigate how they are essential for cell survival and growth. Moreover, the experimental approaches mentioned above utilize these proteins to generate biorecognizable surfaces to promote integration of the material as well as to direct stem cell differentiation by tuning material properties. Therefore, these simple protein constructs still hold importance in engineering biomaterials.

2.2. Biomaterials made from combinations of purified ECM proteins

ECM proteins like fibronectin, elastin, entactin, and laminin lack the material properties needed for generating macroscale biomaterials. Thus, purified ECM proteins are commonly mixed with other native proteins, such as collagen and fibrinogen, to produce more structurally sound biomaterials. These composite biomaterials provide structural integrity and biomolecular cues that can be easily manipulated both *in vivo* and *in vitro*. In an early attempt to mimic the basement membrane, laminin-entactin complexes were added to a collagen scaffold. This resulting material induced greater microvessel formation *in vitro* (Nicosia et al., 1994). In recent years, a basement membrane mimic containing laminin-111, collagen IV, entactin, and heparin sulfate proteoglycans was shown to support endothelial progenitor cells to form tubular structures and bone-marrow derived stem cells to form capillary-like structures (Arnaoutova et al., 2012). A biomaterial composed of collagen and laminin augmented with chitosan was shown to support the viability of circulating angiogenic cells (McEwan et al., 2016). Different mechanical and biochemical properties of these proteins provided multiplex signals and enhanced the biomaterial's capability to engineer cell functions through novel special arrangements, such as layer-by-layer assembly (Mauquoy and Dupont-Gillain, 2016) and homogenous gel formation (McEwan et al., 2016). These laminin-containing composite biomaterials could also support multiple cell behaviors including angiogenic function both *in vitro* and *in vivo.* Similarly, Floren and Tan (2015) explored the effect of multiprotein materials made of collagen, fibronectin, laminin, and elastin on MSC differentiation. By modifying the material properties, they found a correlation between the elasticity of the material and the extent of MSC vascular commitments.

Fibrin and fibrinogen matrices, harvested from the body's clotting cascade, have been used as substrates for cell expansion *in situ* (Stevens et al., 2017) and as delivery vehicles for cells and growth factors (Whelan et al., 2014). When fibronectin was mixed with fibrinogen, the

resulting material possessed a greater elasticity (Okada et al., 1985) due to the inter-linked spatial arrangement of the fibronectin and fibrinogen network. This elasticity was found to be more relevant for directing cell functions (Engler et al., 2006). Gelatin, a biopolymer derived from denatured collagen, can be formed into a biomaterial via various methods including phase separation, electrospinning, and solvent casting (Hoque et al., 2014). An injectable synthetic ECM composed of gelatin, hyaluronan, and chondroitin sulfate supported the proliferation of encapsulated NIH3T3 cells and induced matrix deposition by these cells *in vivo* (Shu et al., 2006). Bovine gelatin displayed lower tensile stiffness compared to collagen, but interacted with soluble elastin with higher affinity, favoring fibrosarcoma (HT-1080) cell line adhesion and growth (Grover et al., 2012). Recently, a multi-compartment system composed of keratin, fibrin, and gelatin was constructed as drug delivery vehicle to release encapsulated substances, such as Mupirocin and Curcumin, in a controlled manner. The fabricated material was capable of accelerating dermal wound healing in a silicone splint animal model by releasing therapeutic agents, facilitating gas exchange, and absorbing exudate (Singaravelu et al., 2017). Other materials that focus on utilizing biopolymers for material backbone, such as polysaccharides and glycosaminoglycans (GAGs), have been reviewed extensively by others (Andersen et al., 2015; Custódio et al., 2014; Lutolf and Hubbell, 2005; Van Vlierberghe et al., 2011).

The building blocks for these multi-protein systems are purified ECM proteins. By combining several of these naturally derived proteins, researchers can adjust the material properties to expose epitopes for biorecognition and induce desirable cellular behaviors. By employing various fabrication methods, different proteins can be layered to create multiplex architectures in engineered biomaterials.

2.3. Cell-derived ECM biomaterials

Even with the most advanced engineering tools, extracted and purified proteins cannot capture the three-dimensional complexity and spatial presentation of growth factors found in native tissue. To create native-like structures, cells like fibroblasts and ASCs were shown to deposit collagen-enriched ECM *in vitro* when treated with L-ascorbate 2-phosphate (A2-P) or growth factors (Franceschi et al., 2009; Reichenberger et al., 1999). The resulting ECM could be decellularized to provide a cell-free construct capable of modulating cell functions (Pérez-Castrillo et al., 2018; Yu et al., 2018). This method of generating ECM was first adopted to produce native matrix for investigating cellular functions *in vitro*. Specifically, primary lung fibroblasts were stimulated by TGFβ−1 and TGFβ−3 to produce ECM that captured some features of native tissue and was used to model aspects of lung fibrosis (Reichenberger et al., 1999). Similarly, by spatially arranging fibroblasts, Wilks et al. (2018) employed normal human dermal fibroblasts to produce highly aligned matrix in a ring shape by using a toroid apparatus. Once decellularized, this matrix instructed fibroblasts to realign with the acellular scaffold. Multiple studies showed that ECM derived from fibroblasts reduced MSC proliferation and levels of stem cell markers via α2 and β1 integrins, while promoting chondrogenic differentiation of MSCs *in vitro* (Dzobo et al., 2016; Zhou et al., 2016). The approach of producing physiologically relevant ECM components has opened other avenues to interrogate the tissue microenvironment. ECM produced by papillary fibroblasts, reticular fibroblasts, and dermal papilla fibroblasts isolated from patients

produced matrices that differentially affected the functions of seeded keratinocytes (Ghetti et al., 2018).

Decellularized matrix produced by stem cells shows great potential for maintaining stem cell multipotency and inducing a particular lineage (Antebi et al., 2015; Lin et al., 2012; Ng et al., 2014; Rakian et al., 2015). The following examples highlight this feature of *in vitro*-derived ECM produced by stem cells. Acellular matrix from fetal mesenchymal stem cells (fMSCs) supported MSCs growth and expansion *ex vivo*. Specifically, MSCs seeded on the fMSC-derived matrix exhibited osteogenic, adipogenic, and chondrogenic markers (Ng et al., 2014). ECM derived from human umbilical cord MSCs was able to increase MSC proliferation compared to tissue culture plastic. More importantly, MSC-derived ECM improved MSC survival under oxidative stress by inducing the expression of intracellular antioxidative enzymes (X. Liu et al., 2016; Zhou et al., 2018). Decellularized ECM derived from placenta MSCs supported the proliferation and growth of MSCs and induced the cells into osteogenic differentiation (Kusuma et al., 2017). Finally, ECM derived from ASCs and bone marrow stem cells (BMSCs) directed these two types of stem cells to either a chondrogenic or osteogenic phenotype, respectively (Pérez-Castrillo et al., 2018).

Aside from *in vitro* applications, CDM offers a biocompatible material that can transiently support cell adhesion and viability, thus extending the effective duration of a cell therapy. ASCs have been explored for the repair of damaged tissue (Traktuev et al., 2006), including cardiac tissue (Przybyt et al., 2015), dermal tissue (Yu et al., 2018), and cartilage tissue (Pizzute et al., 2016). Similar to fibroblasts, ASCs were reported to produce abundant ECM following A2-P treatment (Arslan et al., 2018; Yu et al., 2018). ASCs treated with 250 μM A2-P not only deposited dense ECM, but also displayed enhanced stem cell markers critical for proliferation and downstream differentiation at the wound site. The stem cell sheets upregulated CTRP3 expression in ASCs, and the conditioned media suppressed TGF-β1 and TNF-α expression from macrophages. When transplanted as a “living” material onto full thickness dermal wounds, stem cell sheets provided a longer therapeutic effect than cells alone (Yu et al., 2018). Trottier et al. combined ASC cell sheets with keratinocyte and dermal sheets to produce a three-layered skin substitute composed of simulated epidermis, dermis, and hypodermis. When applied *in vivo*, the skin substitute developed a well-differentiated epidermis and induced cell proliferation as detected by Ki-67 (Trottier et al., 2008). A2-P preconditioning of stem cells was also shown to help regenerate tissues such as cartilage (Pizzute et al., 2016) and tendon (Lui et al., 2016). It is believed that the underlying ECM produced from these treatments provides the essential mechanical and molecular signals that enhance stem cell function in cell therapy.

2.4. Tissue-derived ECM biomaterials

The process of engineering biomaterials using tissue-derived ECM has been facilitated by advances in decellularization. When these techniques were used, tissue-derived ECM was able to retain most of the major protein components and the complex three-dimensional architecture that can serve as a prototyping scaffold for regeneration (Song and Ott, 2011). However, the usage of SDS and harsh mechanical processing in many decellularization protocols can also wash away ECM and matrix-bound proteins and damage the microscopic

structure. The overall effect of the decellularization process on protein preservation and structure retention is detailed in reviews mentioned in section 1. 3.. As a result of excessive depletion of structural proteins, the decellularized organs have different mechanical properties than the native tissue. Structurally impaired decellularized products have been shown to fail *in vivo* or elicit undesirable cellular responses *in vitro* (Petersen et al., 2012; Tsuchiya et al., 2014). More importantly, the ultimate goal of organ decellularization is to provide an alternative source for transplantation. The immune response of the host is the key determinant of the functional outcome of the decellularized construct. A decellularized organ should encourage host cell infiltration and ECM remodeling so that it can be best suited for seamless integration. Dziki et al. (2017) have compiled recent literature on the immunomodulatory effect of decellularized materials. They observed that the initial anti-inflammatory macrophage response and the Th-2 cell response are critical in promoting the viability of the biomaterial post implantation. Evidently, the choice of decellularization process is important not only in retaining the structural and biochemical integrity of the scaffold, but also in ensuring host integration. When proper approaches are taken to decellularize a tissue, the resulting ECM can add layers of both microscopic and macroscopic complexity to biomaterials. Aside from its three-dimensional structure, decellularized ECM can also capture the biomechanical and biochemical modifications present in the native tissue under physiological conditions (Reing et al., 2010). Much of the discussion below concerns recent research on using decellularized native tissue either intact or as hydrogels, powders, surface coatings, and bio-inks that can elicit desirable cellular responses *in vivo* for the purpose of tissue repair.

The dermis is the most abundant source of ECM in the body. Dermal matrix is ideal for skin reconstruction because it stimulates the native dermis microenvironment and contains growth factors that support the repopulation of a variety of cell types (Reing et al., 2010). Additionally, the degradation products from the construct can be readily turned over to produce new dermal tissue (Chu et al., 2018a). Commercial products such as AlloDerm® take advantage of the accessibility of this material. Skin matrices have been made into acellular sheets (Gamboa-Bobadilla, 2006), hydrogels (Wolf et al., 2012), and bio-inks (Kim et al., 2018) for different applications. Specifically, acellular dermal matrix (ADM) has been used for skin reconstruction, especially in breast reconstruction (Krishnan et al., 2014). Acellular dermal sheets mimicked native tissue in elastic properties to provide integration with the surrounding tissue and increased patients' quality of life (Gamboa-Bobadilla, 2006). Use of ADM in sheep showed fibroblast infiltration and vascularization near the implant (Nafisi et al., 2017), implicating ADM in potentially inducing fibroblast and endothelial cell functions for better material integration. ADM was also shown to facilitate dermal wound healing through maintaining ASC survival and directing ASC differentiation into endothelial, epithelial, and fibroblastic lineages that are necessary for closure (Altman et al., 2008; Chu et al., 2018a; Mohamed et al., 2018). As mentioned above, decellularized dermal matrix was also fabricated into a gel form and used as a wound dressing to accelerate wound healing (Wolf et al., 2012), or used as bio-ink for 3D printing in an organogenesis approach (Kim et al., 2018).

Adipose tissue is another plentiful source of ECM. Human decellularized lipoaspirate and its derivatives were reported to have strong mechanical properties (Choi et al., 2011; Ki et al.,

2014) and were shown to support autologous ASC survival and expansion, making it a suitable substrate for *in situ* autologous cell expansion (Young et al., 2011). Decellularized adipose tissue was also shown to support adipogenic differentiation of ASCs (Tan et al., 2017; Turner et al., 2012) and infiltration of these stem cells along with adipose tissue macrophages, which are necessary for adipose tissue regeneration (Kim et al., 2017). Decellularized adipose tissue was enzymatically digested into a thermally responsive hydrogel, which was applied *in vivo* to improve full thickness dermal wound healing (Wu et al., 2018), promoting adipose tissue formation (Adam Young et al., 2014; Kim et al., 2017), and neovascularization (Adam Young et al., 2014). However, it is unclear whether residual growth factors are present in the decellularized adipose construct to encourage cell proliferation and migration.

In the dynamic and biomechanically complex environment of the heart, cells have limited regenerative capacity, as seen following myocardial infarction and other cardiac diseases (Seif-Naraghi et al., 2013). However, decellularized cardiac tissue possesses desirable properties such as presence of the basement membrane (Roderjan et al., 2019), strong mechanical properties, and inclusion of matrisome proteins to support cardiac repair (Pereagil et al., 2018). Whole cardiac ECM (Jeffords et al., 2015; Seo et al., 2017; Taylor et al., 2018), dissected ventricle ECM (Arslan et al., 2018; Baghalishahi et al., 2018; Becker et al., 2018; Duan et al., 2011; Grover et al., 2014; Johnson et al., 2011; Kappler et al., 2016; Seif-Naraghi et al., 2013; Singelyn et al., 2012; Ungerleider et al., 2015; Williams et al., 2015), and dissected pericardial ECM (Bielli et al., 2018; Seif-Naraghi et al., 2012; Sonnenberg et al., 2015) have all been studied for cellular repair post myocardial infarction or for coating other materials. Heart tissue possesses tremendous potential in angiogenesis and in directing the differentiation of human embryonic stem cells (hESCs), MSCs, and cardiac progenitor cells into cardiomyocytes (Arslan et al., 2018; Baghalishahi and Piryaei, 2018; Grover et al., 2014; Seif-Naraghi et al., 2013; Williams et al., 2015). Acellular cardiac tissue was also shown to instruct the endothelial, adipogenic, and chondrogenic differentiation of MSCs (Jeffords et al., 2015; Z. Z. Liu et al., 2016). In particular, a hybrid material made from a 3:1 mixture of myocardial ECM and collagen induced hESC contractility on the matrix and expression of Troponin C, a marker for cardiomyocytes (Duan et al., 2011). However, cardiac tissue incorporated materials have only been tested in animal models for short durations ranging from hours to days (Seif-Naraghi et al., 2012; Singelyn et al., 2012). Long term efficacy experiments are still needed to evaluate the material's ability for cardiac tissue regeneration.

In engineering orthopedic soft tissue, specifically skeletal muscle and tendon, synthetic materials, collagen matrix, and acellular dermal matrix have been extensively investigated (Docheva et al., 2015; Wolf et al., 2015). The use of native muscle tissue has recently been explored for muscle regeneration. Decellularized muscle was found to preserve the anisotropy and ECM components (laminin α2 and fibronectin) necessary to encourage the proliferation of satellite cells, which are critical in restoring muscle function (Mcclure et al., 2018; Zhao et al., 2018). Decellularized skeletal muscle tissues from different parts of the body were shown to retain the distinct mechanical properties unique to the extracted muscle groups (Patel et al., 2019; Wilson et al., 2016), providing a spectrum of material stiffnesses. In a xenotransplantation model, human decellularized skeletal muscle ECM implanted in a

rabbit abdominal hernia model prevented visceral herniation but with limited muscle cell coverage at a 3-week time point (Porzionato et al., 2015). Moreover, studies have found that decellularized skeletal matrix encompasses favorable environmental signals for stem cell myogenic differentiation (Perniconi et al., 2011; Stern et al., 2009). In a rat limb volumetric muscle loss model, decellularized skeletal muscle scaffold embedded with minced autologous muscle tissue showed significant restoration of contractile forces compared to using scaffold alone. This change in cellular behavior was confirmed by the increased expression of MyoD marker (Kasukonis et al., 2016).

Advances in tendon repair and regeneration are lagging in comparison to skeletal muscle therapies due to the avascularity of the native tissue and the strict requirement for mechanical matching (Docheva et al., 2015). Despite multiple high-profile cases where tendon repair with commercial products failed (Lin et al., 2018), there is still effort in the field to engineer ECM-derived materials for this application. For example, decellularized tendon ECM was fabricated into a gel-based scaffold to provide a friendly environment for ASC and MSC growth (Farnebo et al., 2017, 2014; Rothrauff et al., 2017). However, hydrogels do not mechanically match with native tendon tissue. In small tendon defects, tendon-derived stem cells stimulated with connective tissue growth factor and AP-2 were able to deposit ECM and provided a short-term solution, showing more organized alignment compared to unstimulated stem cells or fibrin gel *in vivo* (Lui et al., 2016). For large defects, decellularized tendon slices used in large rotator cuff tear model in rabbits demonstrated short-term improvement of mechanical properties of regenerated tissue, as well as bone matrix formation at the tendon-bone interface (Liu et al., 2018). For additional information the reader is directed to Cheng et al. (2014) and Woo et al. (2019) who have extensively reviewed the use of decellularized tendon and muscle ECM for tissue engineering applications.

The placenta has a unique structure and contains a variety of growth factors and matricellular proteins that support embryonic growth. The innermost lining of the placenta, the amniotic membrane, possesses enriched vasculature and shares similarities with the basement membrane (Becker et al., 2018; Lobo et al., 2016). Because of these properties and its availability, this source of tissue has become a popular choice for tissue engineering. For example, the potential use of placental vasculature for acellular vascular grafts was explored (Schneider et al., 2018). Another exciting study that took advantage of the vasculature in decellularized human placenta to culture hepatic tissue showed promising results in a partial hepatectomy-induced liver failure model in sheep. The existing vasculature and growth factors in decellularized placenta tissue promoted the long-term survival of implanted hepatic tissue with functional results (Kakabadze et al., 2018). Decellularized placenta has also been explored extensively to treat full thickness wounds. The regenerative ability of this ECM-derived biomaterial has been demonstrated in the growth of hair follicles, decreased scarring, and a well-organized dermal and epidermal layer (Choi et al., 2013; Francis et al., 2017; Rameshbabu et al., 2018). A variety of reviews on biomaterials using placenta as a tissue source are available. Niknejad et al. summarized potential applications in both animal models and humans (2008). A full list of ongoing clinical trials involving commercial amniotic products, including NEOX®, Biovance®, and AmnioExcel®, was recently compiled by Moore et al. (2017).

Because of its unique structure, mechanical properties, and pool of growth factors, urinary bladder matrix (UBM) is often used for repair of the urinary bladder, the urinary tract, and hernias (Davis et al., 2017; Pokrywczynska et al., 2015; Rosario et al., 2008; Zografakis et al., 2018) Aside from these common uses, in recent years UBM has been studied to replace ADM for vaginal and abdominal wall reconstruction (Liang et al., 2017; Young et al., 2018). Both authors found that the mechanical similarity between UBM and ADM made it a good candidate to replace the latter as a surgical substitute. UBM-derived hydrogel was shown to attract perivascular stem cells and modulate the host response by downregulating macrophage-derived TNFα, uPA, and IL-1β (Slivka et al., 2014) and promoting the induction of the anti-inflammatory phenotype in macrophages (Meng et al., 2015). In addition, UBM maintained the multipotency of BMSC in culture. Upon induction, BMSCs differentiated into bone, adipose, and smooth muscle cells (Antoon et al., 2012). In summary, UBM is considered a promising surgical graft for various applications. Its abilities to induce an anti-inflammatory response and maintain the multipotency of stem cells present itself as a good carrier for stem cell transfer and implantation.

Decellularized small intestine submucosa (SIS) ECM was developed by Badylak and colleagues and has been significantly investigated for grafting applications in tissues, including blood vessel (Badylak et al., 1989), urethra (Kropp et al., 1998), and bladder (Chen and Badylak, 2001; Lin et al., 2014). Some of the advantages of SIS include its ability to retain the directionality of diffusion and the low porosity found in the native tissue (Andrée et al., 2013). Additionally, decellularized SIS ECM was found to retain higher GAG and laminin content compared to ECM derived from tendon and pericardium (Claudio-Rizo et al., 2017). The construct was found to have abundant fibroblast growth factor (FGF) and transforming growth factor beta 1 (TGFβ−1), which was shown to enhance fibroblast migration and matrix integration in models of both ligament (Fisher et al., 2012; Liang et al., 2015) and cardiac repair (Mewhort et al., 2017). SIS ECM has also shown therapeutic potential in mucosa regeneration. For example, it induced reepithelization in patients who received esophageal circumferential resection (Badylak et al., 2011). When encapsulated with gingiva-derived mesenchymal stem cells, SIS ECM induced regeneration of tongue myomucosa (Xu et al., 2017). SIS matrix also restored the mucosal barrier in an ulcerative colitis model by encouraging the pro-inflammatory phenotype of macrophages (Keane et al., 2017).

Other tissue-derived materials for engineering cell functions are also on the horizon, including omentum-derived ECM for cardiac cell delivery (Shevach et al., 2015), brain-derived ECM for inducing a pro-inflammatory macrophage phenotype (Meng et al., 2015), and liver-derived ECM for bile duct formation (Lewis et al., 2018).

2.5. Diseased and modified ECM biomaterials

Disease and genetic mutations can result in changes in molecular ECM structure and the functions and secretome of the cells residing in the space (Mor-Yossef Moldovan et al., 2018; Robert and Johnson, 2001; Walraven and Hinz, 2018). In addition, matrix remodeling, often accompanying disease progression, is associated with changes in the level of soluble factors such as TGFβ (Doyle et al., 2012), matrix metalloproteinases (MMPs), and cross-

linking enzymes (Argyropoulos et al., 2016). Preparation of ECM constructs from diseased tissues provides an additional investigational tool to determine the relative contribution of abnormal ECM to cellular reprogramming and pathological features. In some cases, decellularized constructs displayed pronounced biophysical changes during the progression of the disease. For example, decellularized lung fibrotic tissue revealed the heterogeneity of stiffness in the diseased tissue, showing a pattern of focal spreading of fibrotic tissue deposition (Melo et al., 2014). In another case, decellularized lungs from patients with chronic obstructive pulmonary disease (COPD) did not support the long-term survival of bronchial epithelial cells, endothelial progenitor cells, MSCs, and lung fibroblasts. However, when the cells were plated onto tissue culture plates coated with homogenized ECM, there was no difference in survival between normal lung ECM and disease ECM, suggesting that the three dimensional ECM structure was abnormal in the COPD lung (Wagner et al., 2014). Decellularized cardiac tissue post myocardial infarction showed significant remodeling events and inhibited MSC differentiation into the myogenic lineage due to increased stiffness (Sullivan et al., 2014). Decellularized tissue taken from organisms in normal and diseased states enable the isolation of the ECM component and can reveal how three-dimensional structure is altered and in turn influences cellular function during disease progression.

Similar to diseased tissues, cells isolated from disease models produce altered ECM that is useful in analyzing the microenvironment of a variety of diseases such as fibrosis, cancer, and diabetes, and the disease CDM can offer new knowledge on how the tissue microenvironment influences cellular function and disease progression. Matrix derived from subpopulations of patients' dermal fibroblasts (papillary fibroblasts, reticular fibroblasts, and dermal papilla fibroblasts) contained distinct fibers that were also observed in the tissue. These fibroblasts maintained "memories" that instructed the intracellular machinery to produce highly or randomly organized ECM fibers (Ghetti et al., 2018). When these matrices were repopulated with cells, scientists were able to reenact the cellular response *ex vivo* by analyzing cell functions, the production of secreted factors, and gene expression (Hedström et al., 2018). Moreover, analysis of ECM derived from tumor associated fibroblasts (Amatangelo et al., 2005; Castelló-Cros and Cukierman, 2009) and lymphatic endothelial cells (Ungaro et al., 2009) allowed the identification of ECM properties and growth factors that were essential for metastasis. Additional research on matrix in aging and diabetic conditions have elucidated how dysregulated ECM can facilitate disease progression. Specifically, when compared to young dermal fibroblasts, aged fibroblasts secreted less HAPLN1, a hyaluronic and proteoglycan link protein, leading to aligned ECM fibers that promoted tumor metastasis (Kaur et al., 2018). By using cell-derived ECM, scientists were also able to study the effect of obesity, a key risk factor for breast cancer, on tumor development and progression. Adipose stromal cells (ASCs) isolated from obese animals displayed an enhanced profibrotic phenotype with elevated levels of a-SMA and fibronectin. As a result, the ECM produced by diabetic ASCs showed a linearized pattern with partial unfolding and higher stiffness. Additional experiments performed on human breast cancer cell line MDA-MB231 showed that diabetic ECM promoted breast tumor cell growth via the YAP/TAZ pathway (Seo et al., 2015). These studies highlight the potential offered by studying CDM in the context of various diseases.

Tissue-derived biomaterials are normally extracted from healthy donors. However, genetic engineering offers an alternative for modulating cell functions through changing matrix composition. Galactosyl-α(1,3) galactose (alpha-gal) is a key player in IgE binding and the immune response (Steinke et al., 2015). In principle, biomaterials from alpha-gal knock-out (KO) animals should reduce the extent of immune rejection. An ECM sheet and an ECM hydrogel derived from alpha-gal deficient porcine tissue were used to treat a transected ACL goat model. The ECM sheet and the hydrogel showed increased neo-tissue generation around the injury site compared to a suture-only control group (Fisher et al., 2012). However, the immunological benefit of this material could not be fully interpreted because a wild type construct as the control was not included. Thrombospondin-2 (TSP2) is a matricellular protein that influences multiple processes including collagen assembly and angiogenesis (Calabro et al., 2015). Matrix derived from TSP2-KO animals displayed impaired von Willebrand factor adhesion, which was associated with resistance to thrombosis (Kristofik et al., 2016, 2017). Acellular dermal matrix developed from TSP2-KO mouse exhibited a greater pro-migratory effect and an enhanced healing ability in a diabetic animal model with greater vessel maturation compared to matrix derived from wild type animals (Morris et al., 2018). Similarly TSP2KO skin-derived hydrogel displayed altered mechanical properties and improved healing of skin wounds in diabetic mice (Morris et al., 2018).

ECM decellularized from diseased tissue can draw out parts of the underlying mechanisms of cellular dysfunction by recreating the ECM environment *ex vivo*. Additionally, genetically modified matrix holds tremendous potential in eliciting desired cellular responses for soft tissue regeneration.

2.6. ECM-polymer coupled biomaterials

Tissue- and cell-derived ECMs display enhanced host response and integration in comparison to synthetic materials. However, in most cases, their fast reabsorption prevents them from providing long-term structural support. To overcome this limitation, synthetic polymers capable of being made into organized meshes and fibers have been combined with native ECM (Fu and Wang, 2012). These polymer-ECM coupled materials, by combining the chemical stability of synthetic polymers and the biocompatibility of ECM proteins, have been shown to induce long-term cellular programming (Shu et al., 2013).

Purified ECM protein or peptide sequences conjugated to, or coated on, a polymer matrix can exhibit stronger cellular effects compared to synthetic polymers alone. For example, fibronectin domains, when coupled to a PEG scaffold, had a greater pro-migratory effect on fibroblasts in a dermal wound compared to RGD functionalized polymer or unmodified polymer scaffolds (Ghosh et al., 2006). In another example, the basement membrane component laminin-111 conjugated to PEG hydrogel induced satellite cell proliferation and myogenic differentiation in a muscle injury model (Ziemkiewicz et al., 2018). This composite material was also shown to provide greater structural integrity than laminin alone and elicited cellular responses that were similar to more complex basement membrane-based materials (Arnaoutova et al., 2012). In addition, fibronectin decorated polyvinyl alcohol (PVA) gel shielded the polymer surface for better fibroblast recognition (Nuttelman et al.,

2001). Collagen has also been used in combination with synthetic polymers such as polycaprolactone (PCL) and bioactive glass nanoparticles, and the hybrid material was used as a delivery vehicle for endothelial progenitor cells in dermal wound healing (Wang et al., 2018). In another example, a collagen-alginate composite material was formulated as a cell carrier. It was found that higher collagen content of this material increased its overall elasticity and enhanced the osteogenic differentiation of MSCs (Lee et al., 2018).

Tissue-derived ECM has also been engineered with polymer backbones. PEG material covalently incorporated into myocardial matrix generated materials with a wide spectrum of stiffnesses and degradation rates for directing cellular function (Grover et al., 2014). Through electrospinning, a dermal ECM and poly(ester urethane)urea (PEUU) composite material was formed that induced repair in a full-thickness abdominal defect model (Hong et al., 2011). In a similar manner, decellularized muscle tissue ECM was electrospun with PCL to provide more structural integrity (Patel et al., 2019). When BARD™, a clinical polypropylene mesh, was coated with porcine dermal ECM, it showed a reduced host foreign body response (Wolf et al., 2014). Finally, a PEGylated graphene oxide scaffold containing dermal matrix and quercetin, a dietary bioflavonoid, was able to induce MSC adipogenic and osteogenic differentiation as well as improved diabetic wound healing (Chu et al., 2018b)

The above studies show that synthetic polymers and biopolymers can complement each other to form stable constructs with tunability in material properties, such as porosity, stiffness, and degradation rate, and can additionally be tuned through chemical crosslinking. Based on the properties of the native ECM, composite materials are expected to display increased biorecognition and a reduction in the foreign body response.

3. Conclusion and perspectives

The adoption of ECM-based biomaterials for soft tissue repair has shown great success in animal models and in some clinical settings. Through various fabrication techniques, ECM-derived materials have evolved into a variety of shapes: surface coatings, meshes, hydrogels, cell sheets, and decellularized tissues and organs. Obviously, the increase in available forms of ECM-derived biomaterials widens the pool of potential clinical applications.

Purified ECM proteins provide the basic biocompatibility. Their abundance and rather simple fabrication process allow for their easy adoption in engineering biomaterials. Subsets of ECM proteins, like fibronectin type III domain and laminin-111, are identified as more potent and essential ECM components that can induce a greater cellular response. By combining different ECM proteins, researchers can construct materials that closely resemble the native tissue micro-environment. Matrices derived from cells provide material that is strong enough to use as a delivery vehicle for cell transplantation. These matrices also provide opportunities to investigate the dynamic processes of ECM deposition and modification under diseased conditions *ex vivo*. In addition, cell lines have been genetically modified to produce ECM proteins in large quantity. Thus, CDM provides an alternative for the future of manufacturing biomaterials independent of tissue sources. Tissue-derived ECM provides the three-dimensional structure and growth factors needed for engineering

functional tissues and organs. However, great care is still required when choosing the proper decellularization process to achieve the balance between protein retention and host immune response. Many studies mentioned above have shown that mechanosensing through integrins is critical in maintaining cell survival and directing stem cell lineage. Anisotropic and isotropic properties of ECM have been proven to influence cell proliferation and differentiation as seen in the case of satellite cells cultured on decellularized muscle tissue. On the other hand, decellularized organs, if matching in mechanical properties, can be used to repair defects in tissues different from their native tissue of origin as seen with acellular dermal matrix and urinary bladder matrix. This unique property of tissue-derived constructs allows for repurposing material to combat the shortage of certain organs. Hydrogels derived from this type of ECM retain growth factors and some material properties present in the original source. They have been shown to provide the necessary stiffness and microenvironment for resident cells to infiltrate and populate. More excitingly, using ECM derived from genetically modified animals or conditioned tissue in disease states can reflect the physiological changes that may benefit *in vivo* repair. These methods open unique avenues for studying the role of ECM in disease progression and repair, and potentially provide new therapeutic targets and ways to engineer cell functions. As shown in the previous sections, these ECM-derived materials are capable of instructing cellular behavior, especially MSCs. Table 2 summarizes the effect of recently developed materials on MSC survival, proliferation, and differentiation.

Sources of ECM proteins have shifted from xenogeneic sources to allogeneic, even autologous sources. This adoption lowers the risk of undesirable immune responses. In particular, adipose and dermal tissues -- the most easily accessible sources for ECM proteins -- can be developed into personalized biomaterials for wound dressing or reconstructive repair. A new trend of using genetically modified animals as the source of ECM allows the investigation of the intracellular mechanisms that regulate matrix production and assembly. Animals with gene deletions or mutations can display drastically different matrix morphology, and in the case of the TSP2-KO genetic modification, the abnormal matrices can further induce the regenerative potential of the wound bed, leading to faster wound closure. Other genetic models may also possess interesting matrix phenotypes that can be exploited to engineer cell functions.

Acknowledgements

This work was supported by NIH Grants (GM-072194; HL083895).

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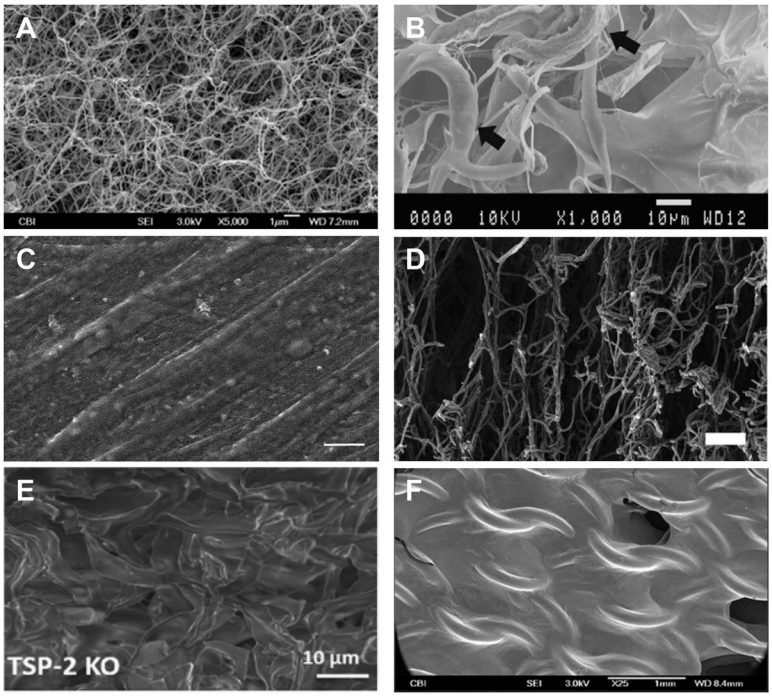

Figure 1.
Representative SEM images of each of the six classes of biomaterials covered in this review.

Table 1

Source for isolating common ECM proteins

ECM Protein	Source	Reference
Collagen	Skin	(McPherson et al., 1986)
	Tail tendon	(Light and Bailey, 1979; Rajan et al., 2007)
	Fish Scale	(Nagai et al., 2004)
Fibronectin	Plasma	(Vuento and Vaheri, 1979)(Ruoslahti et al., 1982)
Laminin	Placenta	(Wondimu et al., 2006)
	Heart	(Paulssons and Saladin, 1989)
Elastin	Aorta	(Rasmussen et al., 1975)

Table 2

The effect of native ECM-derived materials on MSC function

Function	Material	Material Category	Reference
Proliferation and maintanence of stemness	Collagen + polydopamine	Composite (polymer)	(Razavi et al., 2018)
	ECM derived from BM - MSC	Cell-derived	(Rakian et al., 2015)
	ECM derived from BM - MSC	Cell-derived	(Lin et al., 2012b)
	ECM derived from MSC + collagen + hydroxyapatite	Cell-derived	(Antebi et al., 2015)
	Collagen	Purified protein	(Mauney et al., 2005)
	Pericardial matrix	Tissue-derived	(Z. Z. Liu et al., 2016)
	ECM derived from fetal MSC	Cell-derived	(Ng et al., 2014)
	Urinary bladder matrix	Tissue-derived	(Antoon et al., 2012)
Antioxidation	ECM derived from umbillical cord MSC	Cell-derived	(X. Liu et al., 2016) (Zhou et al., 2018)
Neural differentiation	Dermal matrix + reduced graphene oxide	Composite (nonpolymer)	(Guo et al., 2016)
Chondrogenic differentiation	ECM derived from ASC	Cell-derived	(Perez-Castrillo et al., 2018)
	Tendon matrix and cartilage matrix	Tissue-derived	(Rothrauff et al., 2017)
Osteogenic differentiation	ECM derived from fibroblast	Cell-derived	(Dzobo et al., 2016; Zhou et al., 2016)
	ECM derived from placenta MSC	Cell-derived	(Kusuma et al., 2017)
	Collagen + alginate	Composite (polymer)	(Lee et al., 2018)
Adipogenic and osteogenic differentiation Inhibition of myogenic differentiation	Dermal matrix + graphene oxide + PEG + Quercetin	Composite (polymer and nonpolymer)	(Chu et al., 2018)
	Infarcted myocardium matrix	Modified ECM	(Sullivan et al., 2014)
Myogenic differentiation	Myocardial matrix	Tissue-derived	(Arslan et al., 2018)
Angiogenic differentiation	Collagen, laminin, fibronectin, and elastin	Combination of purified proteins	(Floren and Tan, 2015)
Angiogenic under hypoxia	Collagen + chitosan	Composite (nonpolymer)	(Tong et al., 2016)
Endothelial differentiation	Myocardial matrix	Tissue-derived	(Jeffords et al., 2015)