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Review

Extracellular Matrix Coatings on Cardiovascular Materials—A Review

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Abstract: Vascular transplantation is an effective and common treatment for cardiovascular disease (CVD). However, the low biocompatibility of implants is a major problem that hinders its clinical application. Surface modification of implants with extracellular matrix (ECM) coatings is an effective approach to improve the biocompatibility of cardiovascular materials. The complete ECM seems to have better biocompatibility, which may give cardiovascular biomaterials a more functional surface. The use of one or several ECM proteins to construct a surface allows customization of coating composition and structure, possibly resulting in some unique functions. ECM is a complex three-dimensional structure composed of a variety of functional biological macromolecules, and changes in the composition will directly affect the function of the coating. Therefore, understanding the chemical composition of the ECM and its interaction with cells is beneficial to provide new approaches for coating surface modification. This article reviews novel ECM coatings, including coatings composed of intact ECM and biomimetic coatings tailored from several ECM proteins, and introduces new advances in coating fabrication. These ECM coatings are effective in improving the biocompatibility of vascular grafts.

Keywords: extracellular matrix; coatings; cardiovascular materials; surface modification; biocompatibility

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1. Introduction

Cardiovascular disease (CVD) has been the leading cause of morbidity and mortality worldwide for many years, which places a huge burden on health sectors and the economy [1]. Cardiovascular biomaterials can be used in clinical therapeutic devices and implants, such as stents, balloon, artificial heart valve, artificial blood vessel, and occluder, etc. [2–4] (Figure 1), which play an important role in cardiovascular treatment. The clinical use of stents has experienced several stages, such as bare metal stents (BMS, made of stainless steel and cobalt chromium alloys), drug-eluting stents (DES), biodegradable polylactic acid stents and biodegradable magnesium (Mg) alloy stents [5]. At present, iron-based stents, zinc-based stents, and improved biodegradable polylactic acid stents and biodegradable Mg alloy stents are also in the R&D stage [6–9]. In addition, functions related to the biocompatibility of material surfaces, such as anti-coagulation, anti-proliferative, anti-inflammatory and pro-endothelialization, play an important role after implantation. Since endothelialization of cardiovascular prostheses can improve their hemocompatibility, simple surface rapid endothelialization has become a hot spot for cardiovascular device development [10]. At present, the common strategy is to endow the equipment with powerful multi-functions and improve the blood compatibility of the material.

Vascular transplantation is an effective and common method in the treatment of CVD [11]. Tissue engineering techniques are also often applied to the development of vascular materials, with the hope of creating an implant that can support the ingrowth and

maintenance of a patient's own tissue, while the implanted scaffold slowly degrades, leaving behind a functional vascular system [12]. Commonly used materials for vascular grafts are synthetic materials, but their biocompatibility still needs improvement [13]. In contrast, the new extracellular matrix (ECM) coating showed a huge performance advantage [14]. ECM-modified scaffolds have the advantage of mimicking tissue specificity and are thought to better mimic the natural cellular microenvironment in vitro [15]. Functional scaffolds modified with cell-derived ECM have been developed, where the ECM components render the scaffold biologically active and confer some unique functions on the scaffold [16]. This ECM coating-modified scaffold has been proved to improve its biocompatibility. Developing a fully biocompatible coating surface that is effective for cell adhesion is one of the goals of tissue engineering [17]. The ideal scaffold coating, alone or in combination, should have multiple functions, such as promoting endothelialization, preventing the adhesion of inflammatory cells, etc.

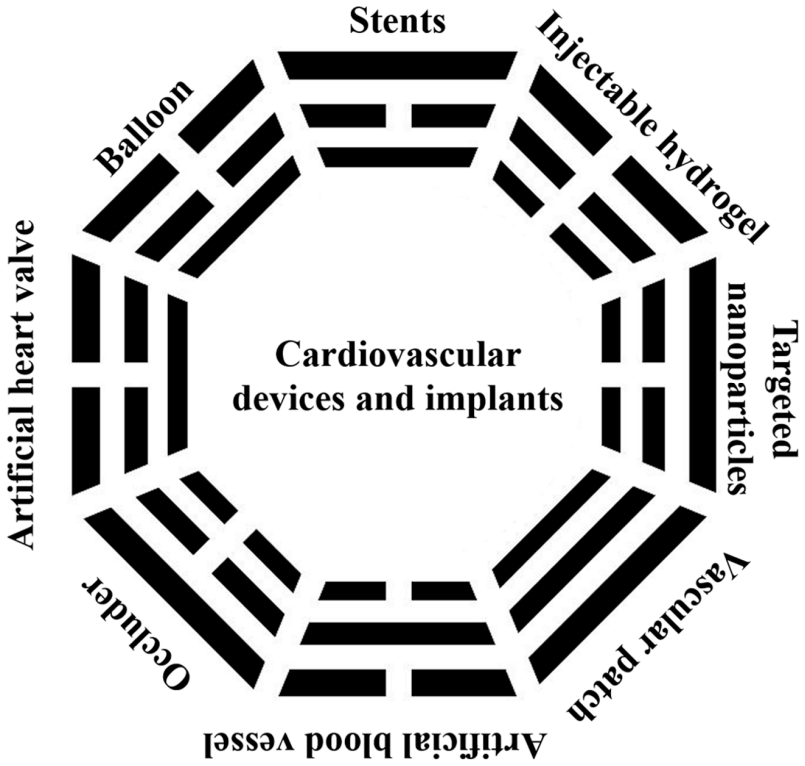

Figure 1. The Chinese eight diagrams to describe the types of artificial cardiovascular devices and implants.

Cardiovascular devices face implant failure, and insufficient endothelialization is one of the main factors. Endothelialization is a process regulated by multiple factors and structures. One method of attracting EC is to precoat the implants with ECM molecules or peptides to promote EC adhesion [18]. An effective approach to improve implant biocompatibility is to functionalize cardiovascular biomaterials with ECM. The ECM is actively involved in various aspects of cardiovascular development and physiology, as well as disease development and progression. The cardiovascular ECM is a complex scaffold of hundreds of proteins that surround the cells of the heart and vascular system and is a key component of the heart and vascular system [19]. The role of the ECM is closely related to its physical and mechanical properties. The ECM coating is closer to the native vascular basement membrane, and the tissue response induced by the implant is milder [20]. As with many other tissues and organs, the application of decellularization methods to obtain acellular ECM scaffolds holds great promise [21,22]. Extensive studies have utilized decellularized ECM from native tissues, or ECM secreted by cultured cells.

ECM-based biomaterials have become mature tools in regenerative engineering, due to their high biocompatibility and biomimetic properties, and bio-scaffolds using ECM materials have become an important medical modality in bioengineering [23–25]. The ECM plays an important role in cardiac repair and regeneration after cardiac injury, and it can be applied as a drug to improve cardiomyocyte proliferation and cardiac regeneration [26]. It has been reported that ECM scaffolds are widely used in medicine, including bone tissue engineering [27], skin tissue engineering [28] and cardiac tissue engineering [29]. ECM-based scaffolds provide a biological matrix with environmental cues that can support the formation of proper vascular tissue. When the scaffold is coated with recombinant human laminin fibers, it supports the attachment and growth of naive stem cells in single-cell suspension [30]. A fibrin-coated pericardial ECM can be used as a material for cardiovascular surgery [31]. The ability of ECM and its components to improve biocompatibility has also been extensively reported [32,33]. Studies have found that ECM coating can improve the adsorption capacity of platelets, reduce EC toxicity, and possibly induce tissue regeneration [34].

There have been numerous experiments investigating new synthetic and naturally isolated coatings. Traditional methods can prepare coatings of corresponding components by separating one or several components from tissue ECM, such as collagen coating, laminin coating. However, the intact ECM appears to be an ideal matrix to promote rapid endothelialization [35]. Coatings with intact ECM components not only mimic the natural cellular environment, but also endow cardiovascular biomaterial surfaces with more functionality. ECM is a kind of biomaterial that can effectively simulate the inherent microenvironment of cells, has good bioactivity, biodegradability and biocompatibility, and has been widely used in vascular grafts. Previous studies have demonstrated that modified ECM coatings can enhance cell attachment and proliferation [35]. The design and modification of ECM coatings have received increasing attention. In this regard, various ECM-related materials have been explored. From tissue-derived ECM 2D coatings, ECM materials have been developed to include recombinant ECM proteins, ECM fragments, and ECM mimetics. Since different components of the ECM play different roles in cellular activities, better characterization of the ECM composition and understanding of its biochemical effects in vivo will help to gain a deep understanding of the research priorities and modification directions of ECM coatings.

2. ECM Materials

2.1. Features and Sources

The ECM is composed of polysaccharides and proteins and it constitutes the microenvironment required by cells. Materials derived from natural ECM are important ingredients of engineered biomaterials designed to mimic cellular and tissue function, and further replace or repair damaged tissue. In some studies, ECM materials have been used in cell culture or injected into vivo for in situ tissue regeneration [36]. For example, several studies have found that ECM-based decellularized myocardial hydrogels can enhance cardiogenesis of cardiac progenitor cells in 3D in vitro culture. In tissues, the ECM offers structural integrity, function, and suitable conditions for cell growth [37]. Mechanical and biochemical cues in the ECM are able to direct many cellular functions. The ECM contains many signaling molecules that are critical for cell behavior, regulating cell growth, polarity, migration, differentiation, and proliferation [38,39]. The ECM plays a crucial role in intercellular signaling, such as tissue regeneration and repair, which are highly affected by proteases and cytokines. Natural ECM has evolved into more complex systems, starting with purified proteins as coatings on the surface of biomaterials, and now there are also cell-derived and whole-tissue-derived constructs. With the advancement of decellularized tissue and isolated cell technology, natural forms of ECM proteins can be better used to create functionally complex biomaterials [40].

ECM can be derived from human or animal organs, tissues or cell cultures. A matrix produced using cells is produced by a single cell type, whereas a tissue-derived ECM is

composed of matrices secreted by multiple cell types. At present, from different organs or tissues, a variety of different types of decellularized ECM can be obtained. This decellularized ECM stays close to the natural tissue or organ structure, which contains natural proteins, soluble factors and cell adhesion ligands [36]. In addition, plant material can also serve as a source of ECM. Due to the advantages of plant-derived materials with fast growth rates and availability in almost unlimited quantities, several studies have used acellular plant materials as potential bio-scaffolds [41,42]. Decellularized plant tissue engineering scaffolds can be obtained by applying decellularization technology to different plants and tissues. Modulevsky et al. used plant-derived cellulose biomaterials to produce implantable scaffolds, and this acellular cellulose scaffold showed biocompatibility in immunocompetent mice [43].

2.2. Cell-Derived Matrix (CDM)

A cell-derived matrix (CDM) is the acellular ECM of tissue obtained through laboratory culture procedures. In contrast to dECM, CDM is derived from laboratory cultured cells/tissues, which are derived from actual animals [44]. CDM and dECM derived from the same tissue can have very similar chemical compositions; however, it is difficult for CDM to have the same physical properties as natural tissues, such as structural organization. CDMs represent biologically active and biocompatible materials that are composed of matrix macromolecules, fibrillar proteins, and related growth factors [45]. The advantages of CDM are the availability of human cell sources, increased tunability of matrix properties and conformations (bulk material or scaffold coatings), and the ability to generate matrices with desirable properties using a variety of somatic and stem cells. Therefore, by designing cell sources and culturing methods, the secreted ECM can be tailored for specific functions, which increases the tunability of CDM.

CDMs are interesting alternatives to traditional sources of ECM. A meaningful method would be to investigate the matrix deposition function of specific cell types, providing an in vitro platform to study cell-matrix interface interactions and their mechanisms. As one of the most commonly used strategies to reconstitute ECM, CDMs have broad applications in biomedical research [46]. CDMs contain complex but organized mixtures of macromolecules, which can imitate various aspects of the natural tissue microenvironment and serve as scaffolding materials to modulate stem cell function. ECM produced by adipose derived stromal cells can enhance tissue-engineered myocardial structures in vitro and promote myocardial remodeling after infarction [47]. CDMs can also be used as a coating by simply decellularizing cells on the surface of biomaterials. Biomaterials based on CDMs are primarily used for bone and cardiovascular repair, and have been explored as cell-delivered cardiac patches, as well as for engineered heart valve replacement and vascular transplantation [48,49].

2.3. Preparation of ECM

To obtain tissue-specific biomaterials, decellularization and isolation techniques can be applied to extract ECM from tissues and organs. Decellularization is the process of separating the ECM from cellular and nuclear material, which has minimal impact on the composition, biological activity, and structural integrity of the ECM [50]. Its primary goal is to remove allogeneic or xenogeneic cellular antigens and other immunogenic components, such as DNA, to minimize the risk of adverse immune responses [45]. This process usually uses physical, chemical, enzymatic and thermal methods. Decellularized ECM, obtained by removing cellular components from native tissues, not only preserves major components and structure, but also prevents potential immunogenicity, and it can serve as a template or scaffold for cell culture [17]. Many clinically used ECM-based materials are produced through the decellularization processes. The following takes CDM as an example to briefly introduce the preparation process of ECM materials.

CDM can be obtained from cells in 2D or 3D culture conditions. The production process of CDMs consists of the following four main steps: cell expansion, seeding, matrix

generation and decellularization. By expansion, to obtain sufficient cell numbers for production; depending on the application, expanded cells can be seeded on different surfaces, such as 2D surfaces or 3D scaffolds [51]. The most important step in production is the creation of ideal culture conditions, whereby the desired properties of the final ECM product can be achieved by systematically optimizing both intrinsic and extrinsic factors. When sufficient ECM is deposited, cellular components can be destroyed and removed from the ECM by chemical, physical or enzymatic treatment and a specific classification can be found in the work reported by Heath et al. [24]. The obtained ECM also needs some post-processing before application, which is further processed into slurries, coatings, hydrogels, etc. ECM post-processing, such as cross-linking, can further alter ECM stiffness or the overall performance of CDM [45]. A recent study also applied ultrasound to ECM materials [52]. Ultrasound can change ECM protein structure through thermal effects and/or mechanical forces, and can also enhance cell-mediated ECM remodeling behavior. This ultrasound-based approach provides an innovative strategy for the preparation of ECM materials, which facilitates non-invasive fabrication and in situ transformation.

ECM can be produced from different cellular sources. The ECM also varies in composition and function depending on the source of cells [53,54]. A single ECM protein cannot fully mimic the complexity of endogenous ECM, and with the in-depth study of ECM, composite biomimetic coatings prepared using multiple ECM components have been shown to achieve better results. The strategies based on molecular self-assembly have received increasing attention, aiming at producing synthetic matrices with multi-component structures and high-level compositional definition. Work in the field of self-assembly synthesis of ECM has mainly focused on peptides or peptide derivatives, and self-assembly can be used to meet the functional requirements of complex ECM [55]. The combination of ECM materials and 3D printing technology is helpful for the construction of in vitro organ models [56]. The emergence of ECM-based bio-inks shows the great potential of 3D printing to build ECM-mimicking scaffolds [57]. Processing of decellularized ECM into microparticles, which are then reconstituted into hydrogels, also expands the range of potential applications [58,59]. For example, a thin coating of ECM through layer-by-layer (LbL) deposition on the cell surface can enhance cell viability and improve tissue function [60].

The production techniques for ECM coatings on biomaterials depend on the property of the devices and implants. Surface self-assembly was the main method to prepare ECM component coatings on the surface of cardiovascular materials for a long time in the past, especially since the LbL self-assembly technology can make the ECM coating more evenly distributed on the surface, but its disadvantage is that with the increase in different layers, the stability of the coating will gradually decline at a turning point [61]. In comparison, it is simpler and more stable for different ECM components to be blended and self-assembled to the material surface as required [62]. The distribution, morphology and behavior of cells on the surface can be controlled by stamping ECM components onto the surface of materials with polymer stamps. For example, the ECM micro-stripes with the width of 25 μm can regulate the morphology of vascular endothelial cells to grow as ifunder the action of blood flow shear stress in vivo [63]. The above coatings can be prepared by chemical reaction, electrostatic interaction, hydrogen bonding or physical adsorption, according to the binding requirements of membrane base. However, due to the long time-consuming process, it is generally not suitable for the preparation of ECM coatings on the surface of small-scale biodegradable devices, such as Mg-base stents. Facing this situation, the spraying method is a good choice, which can complete the preparation of devices' surface coating in just a few minutes [64]. Generally speaking, 3D printing technology can accurately prepare ECM coatings for the surface of devices. However, for some complex surfaces, it also has certain limitations, such as the inner surface of vascular stents. In addition, 3D printing technology is usually used for precision processing of a small number of devices, which is not suitable for large-scale industrial production.

3. Chemical Composition of ECM

The ECM is composed of complex three-dimensional structures and functional biological macromolecules, and it is a unique tissue-specific microenvironment. The protein components of ECM play the roles of ligands for various signaling receptors, such as integrins [65]. The ECM is an important support for vascular endothelial cells (EC), and in the long-term interaction of cells with materials, the ECM can influence cell behavior. The binding of ECM proteins (such as type I collagen or fibronectin) to topographic factors can have different effects on cell processes [66]. The ECM not only ensures the structural strength and elasticity of blood vessels, but also controls the development and stability of the vascular system. Therefore, the ECM is a very important part of the cardiovascular system.

Most vasculature consists of three layers, including adventitia, tunica, and intima [67]. The adventitia is mainly composed of collagen fibers and fibroblasts. The tunica is composed of elastic fibers and smooth muscle cells (SMC), which are responsible for adapting to different blood pressures by contracting and relaxing. In the inner layer, the intima, consists of a thin non-proliferating (quiescent) monolayer of squamous EC that forms the endothelium, largely leaving blood flow undisturbed. Adjacent layers are separated by elastic layers; the outer and middle layers are separated by an outer elastic layer, and the inner and middle layers are separated by a composite of the inner elastic layer and basement membrane. The intimal layer consists of the innermost basement membrane and the substrate below it. The basement membrane provides dynamic hemostasis regulation and is essential for maintaining a confluent, functional monolayer of EC. Basement membranes and placodes are composed of multiple components that can influence cell phenotype and promote cell adhesion [68]. The vascular basement membrane is a lamellar structure composed of various ECM molecules that controls not only the remodeling of the vascular network but also the mechanical stability of the vascular system [69,70]. It is closely related to the occurrence of diseases [71].

As can be observed from the above, the components of ECM are very complex, and each component protein has different effects on cells [72,73]. Due to the important biochemical role of ECM in cells, understanding the composition of ECM and its interaction with cells is crucial for the preparation, modification, and innovation of ECM coatings, which is conducive to the design of ECM materials that are more suitable for medical needs. Of course, due to the complexity and biochemical properties of ECM components, the proteomic characterization is challenging, and it is still impossible to accurately and exhaustively understand the full picture of its composition and function [74]. Combined with numerous existing research results, we mainly introduce several major components of the ECM.

3.1. Collagen

Collagen is the most important component of ECM, and it provides not only tensile strength and cell adhesion, but also structural properties and elasticity to the tissue, which are involved in the formation of a fibrous network [75]. The rope-like structure of collagen resists tension by bearing stress. Therefore, collagen is critical to the substrate, as it provides significant biochemical signals and mechanical strength for cell adhesion and migration.

Although 28 types of collagens have been identified, collagen type I and IV are the most prevalent types found in the cardiovascular system. Collagen provides a three-dimensional environment for cells to support cell growth and influence the morphology and function. Type I collagen is the most abundant component among the cardiac ECM, with a well-described composition-function relationship, conferring strength and stiffness to heart and vascular tissues [76]. Type IV collagen is a specific ingredient of the basement membrane, and its network bonds to the laminin network through nidogen and perlecan. Depletion of type IV collagen results in increased fibronectin expression and extracellular deposition, followed by rearrangement of long, parallel fibrils. Exogenous type IV collagen can restore basal levels of fibronectin deposition, suggesting that type IV collagen may act as a regulator of fibronectin fibril growth.

3.2. Laminin

Laminins can self-assemble into sheets and are essential components of the basement membrane, and can also bind other ECM components together through cross-linking, so they are an important ECM cross-linker. In addition, laminin also enables the ECM to interact with different types of cells through its binding sites with cell surface receptors. Some studies have found that laminin can play critical roles in a variety of functions, such as cell adhesion, cell differentiation, and phenotypic stability. Laminin exerts multiple important functions in the central nervous system by interacting with integrin and non-integrin receptors [77]. Laminin expressed by EC promotes vascular stability and EC morphogenesis [78]. Some laminin modifications may lead to EC dysfunction, thereby promoting the development of atherosclerosis [79]. The laminin network self-assembles on the EC surface and is thought to trigger basement membrane deposition.

3.3. Fibronectin

Fibronectin is a glycoprotein and it is a dimeric structure formed by two polypeptide chains. There are two forms of fibronectin, soluble fibronectin and insoluble fibronectin. In addition, the fibronectin can bind to cells and promote adhesion to other components. This is primarily through the functional and structural domains of the collagen triple helix denaturation regions, and through specific binding domains that bind to heparin and fibrinogen. In conclusion, fibronectin provides a substrate for complex interactions with EC and their environment.

Previous findings have suggested that fibronectin and its receptors are required for vascular formation, and recent studies have further demonstrated that fibronectin is an important signaling molecule for vascularization and is essential for formation of fenestrae in EC of the fenestrated capillary [69]. The interaction between fibronectin and type I collagen suggests that fibronectin may be involved in the arrangement of collagen fibers as a scaffold [65,80].

3.4. Nidogen

Nidogen accounts for a small proportion in the base membrane, but is a crucial factor for organizing ECM, and it can also cross-link other components, including fibrinogen, perlecan, and fibronectin, etc. Nidogen are divided into two types, nidogen 1 and nidogen 2 [18]. Nidogen 1 is important for the attachment and stabilization of self-assembled layers of laminin and type IV collagen; nidogen 2 can also bind components of the basement membrane. There is also evidence that nidogens may contribute to the maintenance of capillary integrity [81].

3.5. Glycosaminoglycans and Proteoglycans

Glycosaminoglycans (GAGs) not only act as ligands for other ECM macromolecules and cellular integrins, but also retain water and interact with biological mediator proteins [82]. At low concentrations, GAGs form a gel, which allows the ECM to resist compressive forces by hydrating and filling the extracellular space. GAG chains can be covalently linked to core proteins to form proteoglycans. The abundant proteoglycans in the ECM can modulate the activity of the secreted ECM by binding to proteins. In addition, they can also change conformation or block binding sites, thereby controlling the transmission of chemical signals from cell to cell. Several proteoglycans are secreted as transmembrane proteins, while others can also act as a receptor for ECM proteins. In addition to being responsible for hydration, GAGs and proteoglycans also play important roles in other cellular behaviors, such as regulating ECM–EC interactions.

GAG play an essential role in tissue engineering. Since different sources and types of biomacromolecules with different biological roles can be included, the combination of GAGs with other polymers can better mimic the multicomponent and multifunctional configuration of native ECM [83]. GAGs are tunable gel components that can modulate collagen fibril formation, hydrogel properties, and guide cellular behavior. Among them,

hyaluronic acid (HA) has a very high molecular weight (MW) GAG, which has been widely applied in various aspects of the biomedical fields (Figure 2) [84]. Collagen hydrogels, containing both modified and unmodified HA, show great promise in tissue engineering. This combined approach of biomaterials could open up new therapeutic approaches for the treatment of complex diseases [85]. As GAGs become more thoroughly understood, it is believed that their use and ubiquity in the field of tissue engineering will continue to expand.

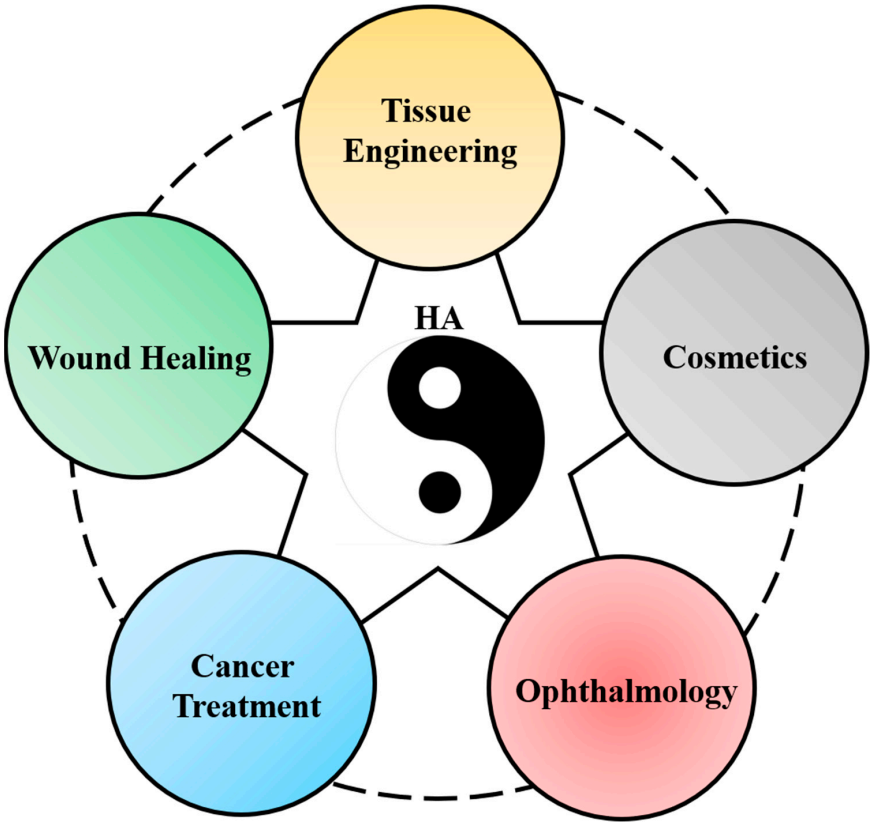

Figure 2. The application of HA, a main component of ECM in biomedical fields [84].

3.6. Elastin

Elastin is one of the main components of the vascular system [86]. It not only provides elastic recovery, but also has crucial influence in mechanical and cellular signaling. The cross-linked network structure of elastin consists of tropoelastin, whose lysine amino acids undergo extensive cross-linking by lysine oxidase immediately after release from cells, followed by condensation to link several side chains. The elasticity of the elastin network comes from its unique structure, and the loose and random coil conformation of the polypeptide chain endows it with good elasticity [87]. Elastin does not form blood clots; thus, the stents and coatings made from it show increased blood compatibility [88]. It interacts with many cell types, and is critical for arterial morphogenesis and controls SMC proliferation. Elastin peptides are chemotactic on EC, and thus have proangiogenic effects [89]. Elastin is a promising candidate for vascular biomaterials or tissue engineering, due to its durable mechanical properties, good association with EC, and inhibition of SMC proliferation.

4. ECM Coatings

ECM coatings are a well-known strategy for improving implant integration. Intact ECM appears to have better biocompatibility and can endow cardiovascular biomaterial surfaces with more functions. Single ECM components have selective, well-defined biological activities and functions [90]. The use of one or a few purified ECM components to

construct surfaces allows for customization of coating composition and structure, potentially resulting in unique functionalities. The hemocompatibility of biomaterials mainly depends on the physicochemical properties of its surface; therefore, surface modification is an effective way to improve hemocompatibility. Surface modification of coatings with biomolecules such as HA, peptides, and heparin can effectively improve the performance of coatings [91–93]. Intact ECM or its single component has natural stability and stiffness advantages to promote the adhesion and functional growth of EC on its surface. This is a kind of dynamic stability. The EC on the material surface will continuously secrete new ECM, according to the environmental response and their own needs. The adhesion of the ECM coatings to the surface of the cardiovascular devices depends on the preparation method and interface bonding mode; the chemically bonded coating is usually stronger than electrostatic bonding, hydrogen bonding and van der Waals force bonding, and the combination of the above forces is stronger than that of physical adsorption, but this law is not absolute.

In this section, several ECM-based coating materials are reviewed (Figure 3). The biomimetic endothelial ECM surface was prepared by EC culture and decellularization, which improved the biocompatibility of the substrate. Inspired by the structure and composition of the native vascular basement membrane, the bilayer coating formed by the ECM secreted by EC and SMC exhibits better biocompatibility, which is expected to address the functional limitations of a single ECM and treat more many clinical diseases. Natural ECM derived from Wharton's jelly (WJ) has shown great potential in vascular engineering and it can be used to prepare standardized coatings. In addition, some mimetic coatings made of ECM proteins exhibit unique functions, due to their special composition and structure. A tailored collagen coating through LbL self-assembly can promote in situ endothelialization and inhibit excessive neointimal hyperplasia, providing a novel approach for developing functional coatings for cardiovascular stents. Synthesizing ECM biomimetic peptide coatings with specific structures helps to overcome stent thrombosis, and further immobilizes biomolecules, such as heparin and glycosaminoglycans, to diversify the coating functions [94,95].

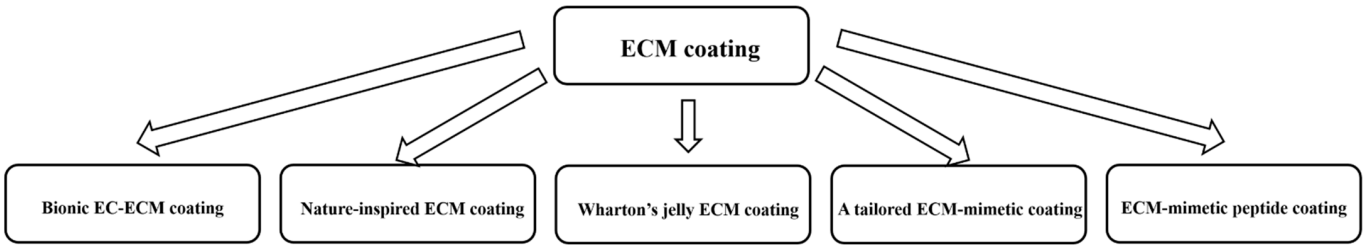

Figure 3. The classification of the types of ECM coatings.

4.1. Bionic EC-ECM Coating

EC play crucial roles in preventing thrombosis; thus, effective re-endothelialization techniques for intravascular implants are important for long-term thrombosis prevention and biocompatibility. A currently recognized and effective method to improve the biocompatibility of cardiovascular biomaterials is the decellularization of the endothelial extracellular matrix (EC-ECM). Li et al. prepared a biomimetic coating composed of endothelial ECM and HA micropatterns (ECM/HAP), which has good blood compatibility and anti-inflammatory properties [96]. In their research, a novel method combining HA micropatterns with EC decellularization was developed; they cultured EC on HA micropatterns and prepared a bionic surface-coated ECM of the elongated and regulated EC by decellularization. The HA microstructure can effectively prolong the cell morphology, induce the secretion of more anticoagulant factors, and limit the contractile phenotype of SMC. Controlling the morphology and ECM secretion of EC by HA micropatterns can significantly improve the biocompatibility of this EC-ECM. The evaluation results further showed that the HA micropatterned endothelial ECM displayed anti-coagulation and en-

dothelialization properties, and inhibited the hyperproliferation of SMC and the attachment of macrophages. This multifunctional ECM/HAP coating can construct biomimetic human endothelial ECM on the surface of biomaterials, and it may provide an efficient method for surface modification of cardiovascular devices. Generally speaking, the immune reactions towards allogenetic or xenogenic cellular antigens are mostly observed in organ or tissue transplantation and above the cellular level, and are relatively rare at the ECM or molecular level. The immune reaction of ECM and molecules to the microenvironment is usually related to the dosage and whether they are antigens. As a coating of cardiovascular materials, a single ECM component is rarely reported as causing an immune reaction. The whole component ECM secreted by cells often causes concern that there may be immunogenicity problems, while HA has the effect of protecting the coating from immune reaction, and the amount of ECM used for surface modification is relatively small. Therefore, immune reaction is not a bottleneck problem that restricts the application of ECM coating on the surface of cardiovascular materials.

On the basis of the above work, by repeating EC culture and decellularization, an idea that could enrich the patterned EC-ECM on the surface of cardiovascular biomaterials came up. Zou et al. prepared a biomimetic EC-ECM surface on polydopamine (PDA)-coated 316L stainless steel by LbL EC culture and decellularization. The surface of this biomimetic ECM was formed by the EC-ECM secreted by patterned EC onto the PDA membrane, and there are fewer platelets and macrophages distributed on the surface of the biomimetic ECM, which indicates that the surface of the new biomimetic ECM has better blood compatibility and anti-inflammatory properties. Compared to surfaces with one and two layers of ECM, surfaces containing three layers of ECM had a more pronounced effect. In addition, the thickness and distribution of macrophages in the new tissues were significantly reduced after PDA modification, and further biomimetic modifications also indicated that more abundant EC-ECM contributes to milder tissue responses. The culture results showed that the three-layer ECM surface demonstrated stronger ability of promoting surface endothelialization. However, in the healthy vascular wall, the ECM of SMC also plays an important role in the adhesion, growth and release of anticoagulant factors of EC. Therefore, the bionic degree of the coating constructed only by patterned EC-ECM is not enough. The vascular basement membrane is composed of ECM secreted by contractile SMC and EC under blood flow shear stress. Therefore, learning from the natural vascular basement membrane structure, building a coating composed of SMC-ECM and EC-ECM may have a better composite function.

4.2. Nature-Inspired ECM Coating

Surface modification with one or more ECM can significantly improve the biological function of the cardiovascular biomaterials. Immobilized proteins or their functional peptides can promote EC growth, while binding mucopolysaccharides confer anti-coagulant, anti-proliferative or anti-inflammatory functions on the surface. On this basis, by modifying the surface of biomaterials with two different ECM components, the surface with a balanced function can be obtained. Inspired by the natural vascular basement membrane composed of ECM secreted by physiological EC and SMC, Han et al. prepared a bilayer ECM coating through successive SMC/EC culture and decellularization, which endowed cardiovascular materials with better biocompatibility [20]. The ECM secreted by EC can make the surface more biocompatible, and the ECM secreted by contractile SMC can better reduce the number of adherent platelets. By controlling physiological SMC and EC by the HA micropattern, followed by sequential culture and decellularization, a nature-inspired bilayer SMC/EC ECM was obtained to modify the material surface. Compared with single-layer SMC-ECM or EC-ECM, the double-layer ECM coating has richer ECM density, larger pore size and different wettability, which contributes to better blood compatibility, anti-proliferative properties, pro-endothelialization, anti-inflammatory function and histocompatibility. In addition, this novel ECM coating can greatly reduce the rate of hemolysis on the material surface, so it has a good inhibitory effect on hemolysis

after implantation. The main feature of this ECM coating is that it greatly improves the reproducibility of the function and structure of the vascular basement membrane on the material surface. The phenotype and function of cells can be controlled in a physiological state by the HA micropattern. The functional advantages of this nature-inspired coating are attributed to its excellent biomimetic properties, which will provide new and efficient methods for surface modification of cardiovascular materials. However, the application of this double-layer ECM is limited because it is not easy to be directly prepared onto the biodegradable or uneven materials. To solve this problem, Liu et al. dispersed the double layer ECM into normal saline using the ultrasonic vibration method, and then self-assembled it onto the surface of biodegradable Mg alloy (ZE21B) (Figure 4), thereby improving the corrosion resistance and biocompatibility of ZE21B [97]. It is unknown whether the process of preparing the ECM solution by ultrasonic vibration will cause losses to its components.

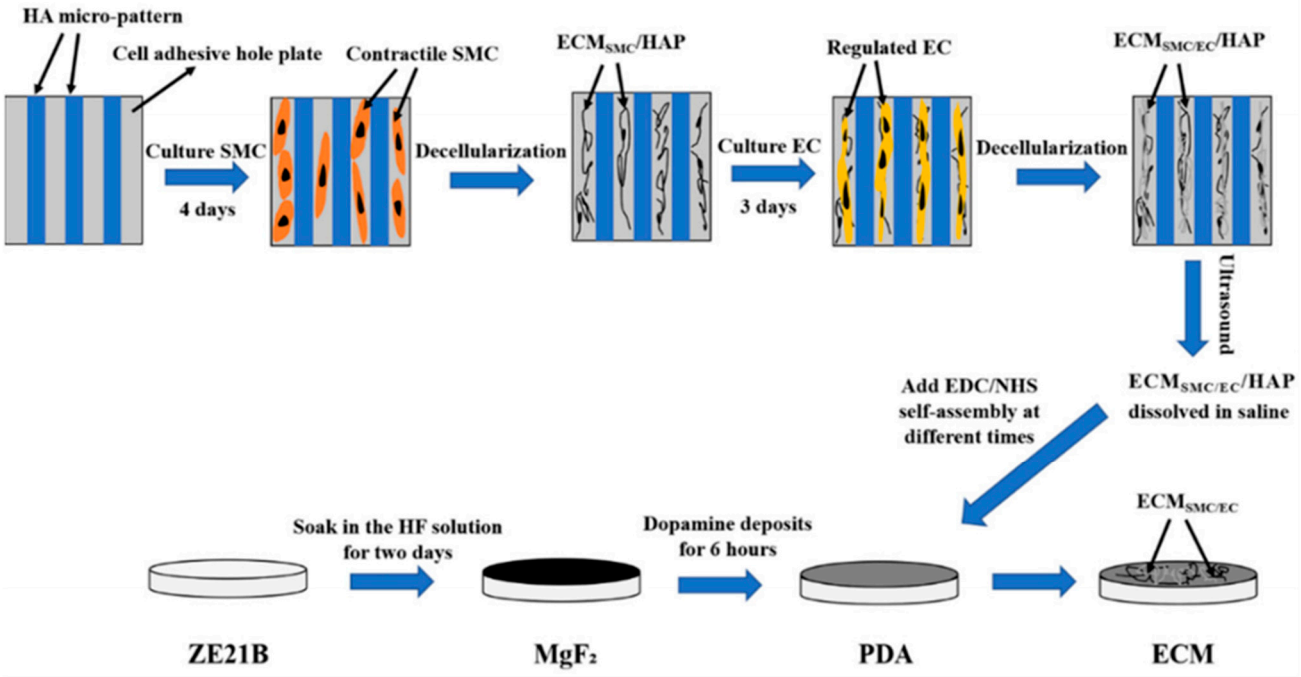

Figure 4. The preparation of the nature-inspired ECM on the biodegradable Mg alloy (ZE21B) surface [97].

Furthermore, heparin is a negatively charged natural polysaccharide that promotes EC proliferation and inhibits SMC expansion. It has been used in the manufacture of vascular grafts, due to its thrombosis-inhibiting properties. The behavior of EC and SMC can be selectively modulated by surface modification of the coating and fixation of an appropriate dose of heparin on its surface. On the basis of the above-mentioned nature-inspired ECM coating prepared from EC and SMC co-culture/decellularization, heparin was immobilized on the ECM coating at an optimized density to selectively promote EC proliferation but inhibit SMC grow and achieve satisfactory blood compatibility [98]. At the same time, the coating also has the characteristics of inhibiting thrombosis, preventing intimal hyperplasia and promoting endothelialization.

Controlling the MW of conjugated HA during surface modification is critical for better biocompatibility. HA, as the main component of the ECM, is a natural biopolymer. This biomolecule has different functions, such as anti-coagulant, anti-proliferative, anti-inflammatory and pro-endothelialization functions, depending on its MW. Low MW (LMW) HA has been reported to be a major player in the thrombosis process, and it also contributes to inflammation [99,100]. High MW (HMW) HA inhibits platelet, SMC, and macrophage adhesion, further conferring anti-coagulant, anti-proliferative, and anti-inflammatory func-

tions on the surface, as well as imparting non-immunogenic properties to the surface, which are critical for implants [101]. However, HA with extremely HMW inhibits endothelial progenitor cell adhesion and EC migration, which is clearly not conducive to rapid endothelialization. Li et al. provided better versatility for cardiovascular biomaterials by preparing HA with gradient MW and controlling the MW of HA on the coating surface [102]. HA with an appropriate MW affects the homeostasis of important pathways in the cardiovascular system, inhibits phenotypic changes in vascular SMC and platelet activation, and promotes the repair and functionalization of endothelial monolayers. This demonstrates the feasibility of coatings with appropriate MW HA for potential applications in the surface modification of cardiovascular implantable devices.

Further research found that a HA nanoparticle less than 200 nm could carry Mg ion into EC, which would inhibit EC apoptosis and promote nitric oxide (NO) release of EC [103]. Our study discovered that the Mg is the main degradation product of biodegradable Mg alloys, which may control the phenotypes of macrophages and the function of EC, further regulating the pro-endothelialization function of the Mg alloy stents (Figure 5) [104]. Thus, a nanocomposite coating was placed onto the Mg alloy to regulate the degradation behavior and the Mg transportation to the EC, SMC and macrophages based on the different requirements of different cells for Mg concentration (Figure 6) [105].

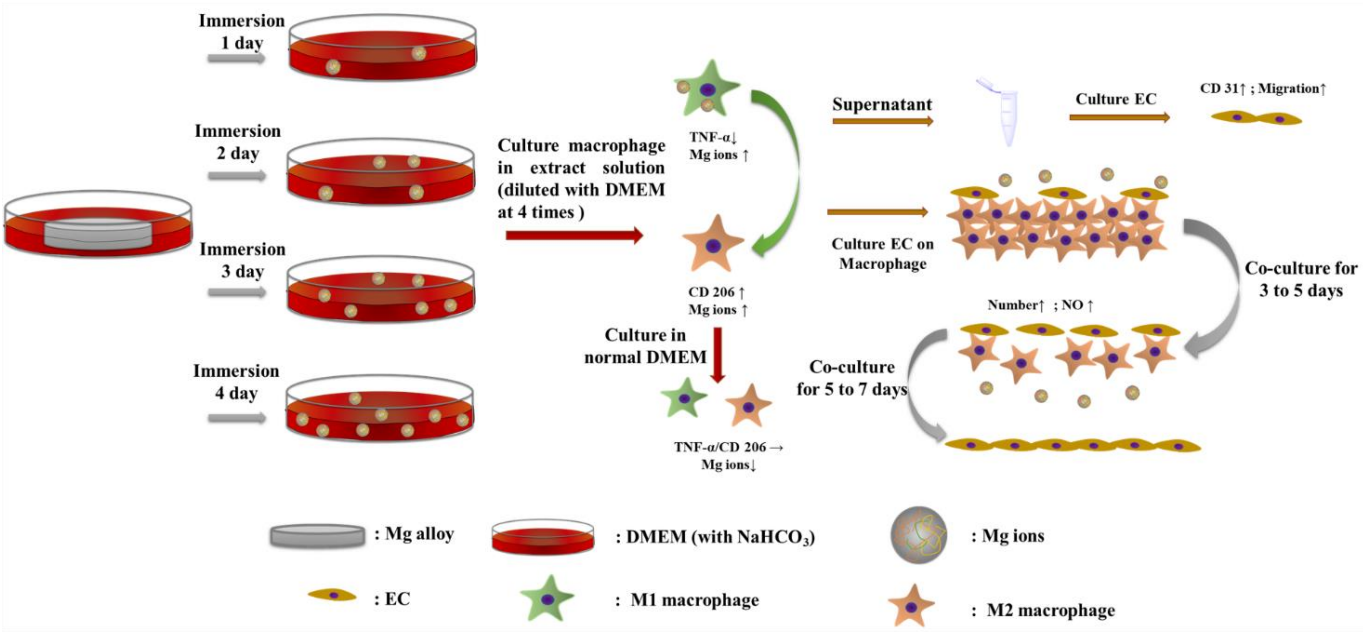

Figure 5. Mg alloy degradation products that regulate macrophages and EC behaviors [104].

4.3. Wharton's Jelly ECM Coating

Human tissue may be a suitable material for the preparation of natural matrices, from which we can extract intact ECM. Hao et al. previously demonstrated that the ECM obtained from Wharton's jelly (WJ) can contribute to MSC culture [106]. Previous studies have also proven that WJ-ECM contains several growth factors, which may promote angiogenesis and vascular cell differentiation [107]. Meanwhile, since WJ-ECM is prepared from human tissue, it does not have any toxicity to cells. In various tissue engineering, WJ-ECM becomes a universal tool to support cell culture. Using native ECM extracted from Wharton's jelly (WJ), Dan et al. report an innovative method for preparing coatings [108]. The mechanical, chemical and enzymatic methods are common methods for ECM isolation. However, simple stirring or chemical dissolution of ECM extracted from WJ tissue is less effective. Here, Dan et al. used trypsin to isolate intact ECM, which not only simplifies the isolation procedure, but also keeps the ECM-containing tissue in a relatively physiological state. Furthermore, WJ-ECM can form a continuous coating on the negatively charged glass

surface, and the ECM concentration determines the thickness and stiffness of the coating. Because ECM is derived from human tissue, the coating does not contain chemicals that are harmful to cells, which is the biggest advantage of this coating.

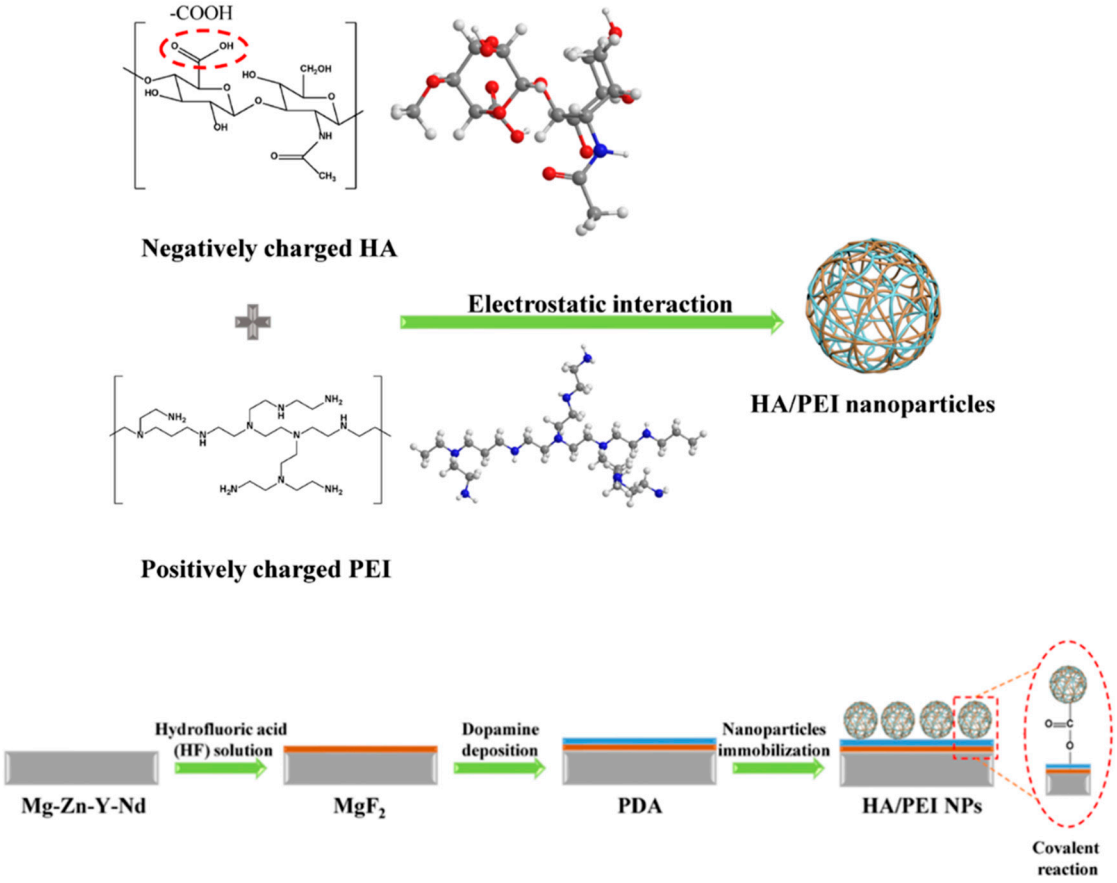

Figure 6. Nanocomposite coating on the Mg–Zn–Y–Nd alloy prepared with HA nanoparticles [105].

The performance of this WJ-ECM coating showed that the WJ-ECM-derived coating could enhance the adhesion and proliferation of EC and human mesenchymal stem cells (hMSCs). Compared to collagen coatings, a higher number of cell adhesions can be observed on WJ-ECM under physiological shear stress. In vascular tissue engineering, biomaterials must provide adequate cellular anchorage against shear stress. In the EC test, the WJ-ECM coating was better than the commercially available collagen I coating for cell anchoring. This suggests that WJ-ECM may promote the endothelium, thereby establishing a suitable continuous layer during vascular tissue engineering. In addition, this new surface shows an interesting phenomenon that the resistance of cells increases under the flow shear stress. Overall, WJ-ECM is a very valuable surface coating, with important applications in the design of biocompatible surfaces in humans.

4.4. A Tailored ECM-Mimetic Coating

As introduced previously in this review, collagen is one of the main components of the ECM. Mixed with other polymers, it is possible to mimic the basic structure of a specific ECM and further obtain the desired function with growth factors [109]. Collagen has been widely used in tissue engineering, but its inherent thrombogenic properties limit its application in vascular devices. The binding affinity to platelets is a major cause of collagen thrombosis, while previous studies have suggested that hydroxyproline (O) may be critical for platelet adhesion and activation. In addition, recombinant collagen not only has better water solubility, but also has a low inflammatory response. Thus, designing recombinant proteins with a large number of cell adhesion motives, but without

hydroxyproline, may provide a new method for developing collagen for blood contact. In recent studies, an ECM-mimetic multilayer coating formed by the assembly of collagen and HA has emerged [110].

Yang et al. developed a recombinant human type III collagen protein (hCOLIII), which contains multiple charged residues and has a stable triple-helix conformation. The results of its assessment showed that platelets lacked affinity for hCOLIII [110]. Furthermore, by depositing the hCOLIII LbL assembly together with HA on the amine-rich PDA-coated substrate, they prepared an ECM-mimetic multi-layer coating. The coating has significant thromboprotective properties. Compared to animal-derived collagen, the use of hCOLIII-tailored ECM-mimetic coatings have advantages in inhibiting platelet adhesion and activation. When the coating was prepared with animal-derived collagen, it showed more platelet adhesion. In contrast, hCOLIII-based ECM coatings effectively inhibited platelet adhesion. The coating showed stable performance after implantation, and the experimental results showed that the composite coating had longer and reliable anti-coagulation ability with the higher coverage of hCOLIII and HA. Furthermore, this ECM-mimetic coating provided a favorable microenvironment for EC to promote in situ endothelialization, which showed the properties of enhancing endothelialization. The quantification of adherent platelets also suggested that hCOLIII may be a custom collagen-derived material, showing potential for use as a surface coating for blood-contacting devices. The emergence of this novel ECM-mimetic coating indicates that the hCOLIII-based ECM coating can be used as a blood-contacting material, with promising application prospects in cardiovascular stents. Moreover, the ECM-mimetic coating has the functions of promoting in situ endothelialization and inhibiting excessive intimal hyperplasia, which provides a new method for the use of collagen materials to develop coatings for cardiovascular stents.

In addition, several materials, including gelatin, fibrin, collagen, and silk, have been used for cardiac tissue engineering. A recombinant spider silk protein has been found to be a promising cardiac tissue engineering material, which can be used for coating and 3D printing, offering many of the advantages of silk materials, such as low immunogenicity and biodegradability [15]. This coating made of recombinant spider silk protein is non-cytotoxic, has no apparent pharmacological properties, and does not prevent cardiomyocytes from adequately responding to extracellular stimuli. In terms of cardiomyocyte adhesion and cell viability, this coating was comparable to the fibronectin coating. Because of these intriguing properties, spider silk proteins offer perspectives for future research that could potentially be used to produce cardiac patches for clinical applications.

4.5. ECM-Mimetic Peptide Coating

Insufficient endothelial coverage of cardiovascular implants is a major risk factor for implant failure, due to thrombogenic enhancement. To enhance cell-material interactions, ECM-inspired coatings were developed to provide EC with tissue-specific signaling molecules that modulate cellular activation states for adhesion, proliferation, and survival [94]. Receptors on the cell surface can recognize ECM molecules and trigger signaling pathways that control cell adhesion, migration, and apoptosis. Conjugating certain bioactive peptide sequences may be an available method to direct the cellular activation of implants to the desired wound-healing mechanisms. By mimicking the natural cellular environment, the ECM-derived peptide coating can enhance the interaction of EC with the scaffold material. Peptide-based biomaterial coatings offer a promising toolbox for achieving multifunctionality.

A new peptide coating is presented by Clauder et al., describing a promising approach to stent coating [111]. It contains three proteins of the ECM, namely elastin, fibronectin and laminin. This study used the method of solid-phase peptide synthesis (SPPS) to synthesize carrier peptides. Orthogonal click chemistry reactions provide an efficient method for the functionalization of ECM-derived peptides that can decorate anchor peptides with one or more adhesion motifs. Furthermore, the tunability of anchoring strength and orientation make this method promising. Clauder et al. synthesized three monofunctional peptides

and one bifunctional peptide in experiments to study the effect of ECM biomimetic peptide coatings on stent endothelialization and hemocompatibility. This peptide coating was blood compatible, causing neither hemolysis nor platelet adhesion. At the same time, cell–surface interactions were synergistically enhanced when two adhesion peptides were presented in one molecule. The effect of bifunctional peptides on endothelialization was stronger than that of the fibronectin coating, which indicated that the artificial peptide coating had more advantages than non-specific protein adsorption. This cell-adhesive peptide coating is not only suitable for bare metal stents, but also for top layer modification of drug-eluting stents. This provides a feasible method for overcoming late stent thrombosis and improving stent integration.

In further work, Clauder et al. proposed modular assemblies consisting of adhesion peptides, heparin, and pro-angiogenic factors, which could serve as biomimetic coatings that are suitable for cardiovascular devices. Integrins can affect the ability of EC to regulate hemostasis [112]. By equipping them with integrin and proteoglycan binding sites, designing mussel-derived surface-binding peptides can enhance endothelialization. Heparin and heparin-binding angiogenic factors are fixed to peptides using modular assembly. A synergistic effect is proposed due to the tight interaction between cytokines and integrins, which emphasizes the interaction between ECM components. Combining these components in functional biomaterial coatings induces synergy and further enhances the regeneration process. This study also demonstrated that the bifunctional peptide coating was superior to non-specifically adsorbed adhesion proteins. This study shows that a coating that incorporates adhesion peptides, glycosaminoglycans, and modulators is a universal tool that can deliver ECM-inspired versatility to biomaterials and facilitate their integration.

5. Summary and Future Directions

The exploration of ECM coatings has undergone a long research phase, and many different types of surface coatings have been developed. ECM coatings prepared by extracts of organs, tissues or cells exhibit higher biocompatibility and have great potential for application in blood-contacting devices. From collagen or fibronectin coatings formed by single components to coatings made of intact ECM, and furthermore, to bilayer coatings formed by ECM secreted by both cells, ECM coatings show increasingly functional diversification. The increasing availability of ECM-derived biomaterials has broadened the range of potential clinical applications. Although peptide-based self-assembly methods mimic larger partial or entire protein structures that can re-build the structure of the ECM, and these complex ECM mimetics possess microstructural motifs and associated mechanical properties that match innate protein complexes, the function of natural ECM is still irreplaceable. In the future, the biomimetic construction of natural coatings on the surface of cardiovascular materials by using a variety of new technologies in terms of all components and structures will endow the surface with more complex biological properties.

However, based on the complex active components of ECM coatings, during the process of cleaning (usually using a buffer, such as normal saline), sterilization (usually using ultraviolet irradiation sterilization) and storage (4 °C or −20 °C), certain changes will be made to its components or component structure. Some of these changes will not influence the overall stability of the ECM coating, while others will cause serious damage to the stability of the coatings, especially the trace components in bionic ECM coatings. Therefore, in future research, in a sterile environment, the fitting of active ECM coatings with cardiovascular implants over a short time to reduce the stability loss caused by cleaning, sterilization and storage should become a direction of industrialization efforts.

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