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Review article

The role of the extracellular matrix in cardiac regeneration

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ABSTRACT

The extracellular matrix (ECM) is a complex and dynamic three-dimensional network that functions as an architectural scaffold to maintain cardiac homeostasis. Important biochemical and mechanical signals associated with cell–cell communication are provided via the reciprocal interaction between cells and the ECM. By converting mechanical cues into biochemical signals, the ECM regulates many cell processes, including migration, adhesion, growth, differentiation, proliferation, and apoptosis. Moreover, the ECM facilitates the replacement of dead cells and preserves the structural integrity of the heart, making it essential in conditions such as myocardial infarction and other pathological states. When excessive ECM deposition or abnormal production of ECM components occurs, the heart undergoes fibrosis, leading to cardiac dysfunction and heart failure. However, emerging evidence suggests that the ECM may contribute to heart regeneration following cardiac injury. The present review offers a complete overview of the existing information and novel discoveries regarding the involvement of the ECM in heart regeneration from both mechanical and biochemical perspectives. Understanding the ECM and its involvement in mechanotransduction holds significant potential for advancing therapeutic approaches in heart repair and regeneration.

1. Introduction

The extracellular matrix (ECM) is a dynamic, complex, three-dimensional network of glycoproteins, collagens, and proteoglycans (PGs) that functions as a mechanical scaffold for cellular structures [1,2]. However, recent research has revealed that the ECM has additional functions beyond its structural role. The ECM can be classified into two primary categories according to its location and structure: the basement membrane, which separates epithelial/endothelial cells and underlying tissue cells, and the interstitial matrix, which forms a porous 3D lattice [3]. Through constant modelling and remodelling, the ECM maintains tissue homeostasis [4]. It interacts with cells through various signals, including chemical, electrical, and mechanical signals, thereby regulating migration, adhesion, growth, differentiation, proliferation, and apoptosis [5].

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After adulthood, some lower vertebrates possess an increased ability to regenerate injured heart muscle. For example, zebrafish have a remarkable capacity for complete heart regeneration within two months after resection of up to 20 % of their ventricular tissue [6]. Cardiac tissues of adult *Xenopus tropicalis* can regenerate in a nearly scar-free manner approximately 30 days after injury [7,8] Similarly, adult axolotls can restore the functional myocardium after partial ventricular amputation through cardiomyocyte (CM) proliferation [9,10]. However, adult mammalian CMs have limited potential for proliferation and regeneration. CM turnover is estimated to reach 0.5 %–2 % per year in both adult human and murine hearts [11]. Adult CMs are terminally differentiated cells, and an imbalance between damage and repair reduces the capacity for regeneration in the heart [12]. The inability to replace lost CMs following the onset of injury results in fibrotic scar formation and negative remodelling, which contributes to poor cardiovascular outcomes. Cardiovascular disease is a significant global public health issue, and there is an urgent need for effective regenerative therapies for injured human hearts [13].

Studies have shown that cardiac pathological conditions are closely associated with alterations in ECM composition. For example, fibronectin (FN) expression is upregulated in myocardial infarction, and the absence of the FN-EDA isoform has been shown to mitigate negative cardiac remodelling and improve cardiac output [14]. Hyaluronan synthesis increases after cardiac ischaemia and plays a crucial role in infarct healing by activating macrophage and fibroblast responses [15]. Furthermore, mechanotransduction plays a vital role in heart regeneration by facilitating the conversion of mechanical stressors into biochemical or electrical signals, which are crucial for cardiac regeneration and the initiation of tissue remodelling. The Hippo pathway and the ERBB2-extracellular signal-regulated kinase (ERK)-YAP mechanotransduction signalling pathway perform key functions in modulating CM progression and increasing heart size, and modulating this pathway promotes cardiac regeneration and improves survival [16–19]. However, the understanding of how ECM mechanics impact cardiac regeneration is still limited. The literature review elucidated the composition and distinctive roles of the cardiac ECM, especially the importance of mechanotransduction signalling pathways during cardiac regeneration, to enhance our understanding and inspire the advancement of regenerative treatments for heart disease.

2. Cardiac ECM under physiological conditions

Under physiological conditions, the cardiac ECM consists of various components, including elastin, collagens, laminin, FN, PGs, glycoproteins, and glycosaminoglycans (GAGs).

2.1. Collagen

The principal structural elements of the cardiac ECM are collagen types I and III. Collagen type I, which accounts for 80 % of total myocardial collagens, primarily develops thick parallel rod-like fibres in the epimysium and perimysium, providing resistance to stretching and deformation [20,21]. Collagen type III, which accounts for 11 %, is found in the endomysium and contributes to the resilience of the ECM [21]. Collagen type IV is the primary component of the basement membrane and associates with laminin, glycoproteins, and PGs to assemble into a meshwork structure that surrounds each CM. The basement membrane maintains the function of endothelial cells and regulates cardiac electrical properties [22,23].

2.2. Fibronectin (FN)

FN contributes to cell adhesion, migration, and intracellular signalling. It performs crucial functions via distinct mechanisms, including embryogenesis, wound healing, and tissue integrity maintenance [24,25]. Knocking out FN1 leads to embryonic death at an early stage of development because of the inability to establish a heart tube [26,27].

2.3. Laminin

Laminin is a heterotrimeric glycoprotein composed of α, β, and γ chains that strengthens the ECM structure by interacting with other glycoproteins. It also participates in intercellular signalling by binding to membrane receptors, such as integrins [28]. In addition, the nonstructural components of the ECM can store growth factors, cytokines, and extracellular proteases, which can be secreted or activated during heart injury [29,30].

2.4. Proteoglycans (PGs)

PGs consist of a core protein modified with one or more covalently linked glycosaminoglycan (GAG) chains. The GAG components are linear polymers of repeating disaccharide units consisting of an amino sugar and a uronic acid. In general, sulfation can occur at several locations of each monosaccharide in the GAG chain, resulting in a strongly negatively charged polysaccharide. This characteristic gives PGs the capacity to chelate, allowing interactions with certain ligands, such as growth factors, proteases, cell surface receptors, and cell adhesion molecules [31]. PGs are divided into four main classes according to the main GAGs they contain: heparan sulfate proteoglycans (HSPGs), chondroitin sulfate proteoglycans (CSPGs), dermatan sulfate proteoglycans (DSPGs), and keratan sulfate proteoglycans (KSPGs). Some PGs require GAG chains for interactions, whereas others rely on core proteins [32]. In addition, non-sulfated GAG hyaluronic acid (HA) does not covalently bind to the core protein. It is a major component of the ECM and regulates the activity of many proteins [33].

These complex molecular structures form a three-dimensional polymer network in the myocardium, facilitating the

interconnection of myocytes, the alignment of contractile components, the mitigation of myocyte overextension and disruption, the transmission of force, and the provision of tensile strength to avoid rupture (Fig. 1). It is not yet fully understood whether intracellular signalling and regulatory processes are involved in heart regeneration. Additional research is needed to clarify the molecular pathways and interactions between matrix proteins and CMs, vascular cells, and interstitial cells.

3. Cardiac mechanotransduction: the correlation between the ECM and the intracellular space

Mechanical stress refers to various mechanical forces that regulate cellular pathways and tissue functions. Typical mechanical forces include hydrostatic pressure, shear stress, cyclic stretch, extracellular matrix (ECM) stiffness and extracellular fluid viscosity [34]. CMs continuously experience different types of mechanical stresses. Mechanotransduction is the conversion of mechanical forces into biochemical cues that trigger various biological processes, including embryonic development, tissue repair, and regeneration [35]. This process involves three main types of molecules: ECM components, matrix receptors, and intracellular structures (Table 1). ECM components, such as collagen, transmit mechanical loads to CMs. Like integrins, matrix receptors form physical connections between the ECM and the cytoskeleton, creating physical connections between the cell exterior and interior. The cytoskeleton transmits mechanical signals within the cell, influencing cell growth, differentiation, and proliferation. The ability of CMs to perceive mechanical signals from the extracellular space is pivotal for the intricate mechanism of heart regeneration. Disruption of mechanotransduction can lead to gene dysregulation and, eventually, heart disorders, including cardiac hypertrophy and fibrosis.

3.1. ECM components

The interaction between cells and the ECM is affected not only by the chemical composition and structure of the ECM but also by its mechanical properties. Collagen imparts tissue material stiffness and tensile strength, whereas elastin endows tissues with extensibility and resilience. In addition, owing to the hydrating properties of PGs (e.g., perlecan and hyaluronan), they provide compressive stiffness to connective tissues. Multiple adhesive glycoproteins, such as fibronectin and laminin, can bind proteoglycans and collagen fibres [36]. The cell must sense and modulate the ECM mechanism to maintain the dynamic balance of the microenvironment.

3.2. Integrins

Integrins are adhesion receptors that exist as heterodimeric transmembrane proteins consisting of α and β subunits. In CMs, the

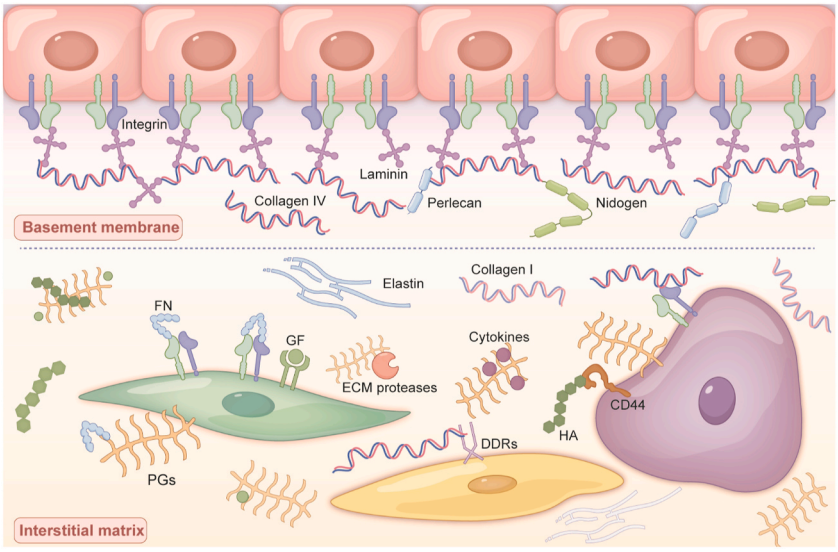

Fig. 1. Schematic depiction of the matrix composition and physiological properties.
The ECM is a noncellular three-dimensional polymer network that exists in all tissues and organs. It serves as a physical scaffold for cellular embedding that initiates vital biomechanical and biochemical signals necessary for tissue differentiation, development, and homeostasis. Collagen accounts for 30 % of the total mammalian protein content and is found in fibril and nonfibril forms. Collagen is synthesized and secreted by fibroblasts, provides structural strength to all forms of the ECM and limits the distensibility of tissues. Glycoproteins mainly include elastin, laminin, and FN, which have diverse functions. Elastin is responsible for conferring elastic properties to tissues that experience repetitive stretching. FN and laminin bind to cell surface receptors (such as integrins) and influence cell adhesion, differentiation, and migration. PGs are composed of a core protein with coupled GAGs and participate in space filling and lubrication. PGs can bind many cytokines, growth factors, and chemokines in the ECM. Owing to their capacity to engage with additional ECM molecules and cell surface receptors and activate a variety of signal transduction pathways, PGs perform essential functions in ECM remodelling and physiological and pathological processes. DDRs: discoidin domain receptors; GF: growth factor; HA: hyaluronan.

Table 1
ECM mechanotransduction proteins and their roles.

Protein or structure	Role
Collagen	Most abundant protein; Endows tissue stiffness, strength, and plasticity
Elastin	Provides extensibility and resilience; Influences the stiffness of collagen fibers
PGs	Extensive hydrationand contribute to the compression resistance; Chelating ligands, such as growth factors and cell adhesion molecules
FN	Binds with collagen to form fibronectin-collagen network
Integrins	Cell surface receptors; Receive signals from ECM components; Transmit mechanical and biochemical signals into cells
Talins, Kindlins, Vinculin	Promotes the activation of integrins; Mediates the anchoring of the cytoplasmic domain of integrins to the actin cytoskeleton
Cytoskeleton	Couple with nuclear envelope; Influences chromatin dynamics, epigenetics and gene transcription

most highly expressed integrin heterodimers are α1β1, α5β1 and α7β1, which are mainly collagens, FN and laminin binding receptors, respectively [37,38]. Integrins are central mediators of mechanotransduction. By connecting the internal cytoskeleton to the ECM, it can monitor cell attachment and the physical properties of the matrix, sense external mechanical changes and generate a biochemical response [39,40]. The activation of integrin signalling and focal adhesion kinase is essential for the significant maturation of human cardiac monolayers [41]. Integrins can enhance sarcolemmal stability, increase muscle regenerative capacity and reduce cardiomyopathy [42]. Although integrins do not have their own enzymatic activity, they are effective for both directional signalling receptors. After binding to extracellular ligands (such as collagen, laminin, or FN), integrins aggregate to form focal adhesions, initiate actin polymerization, and activate a wide range of intracellular signalling pathways. Intracellular signalling is often referred to as outside-in signalling. When the mechanical force exceeds the threshold, the activation domains are exposed. By aggregating a range of adapter and signalling proteins, integrin-linked kinases, Src family kinases, focal adhesion kinases, paxillin and vinculin [43,44], integrins produce a wide range of intracellular signals (e.g., the Akt, MAPK-ERK-p38, and NF-κB pathways) [39]. In contrast to extracellular events, cells can exert contractile forces on the matrix through these adhesions to regulate cell behaviour. Events occurring within the cell can trigger integrins to change their conformation and alter their ECM-binding characteristics. This process is termed inside-out signalling.

3.3. Cytoskeleton

The cytoskeleton has three functions. It provides structural support for cells, connects cells physically and biochemically with the external microenvironment, and helps cells move and change shape [45]. The cytoskeleton mainly controls gene transcription by regulating the nucleocytoplasmic shuttling of mechanosensitive transcriptional coactivators. The most important of these are the Rho pathway effector MRTF and the Hippo pathway, which target YAP/TAZ [46]. Interestingly, the effects of MRTF and YAP/TAZ are very consistent. After their nuclear localization is increased, they both significantly increase matrix hardness or cell stress and reduce the interaction between cells [47,48].

Changes in ECM rigidity and cell morphology can significantly regulate the nuclear localization of YAP/TAZ via the actin-cytoskeleton and Rho-ROCK pathways and regulate cell proliferation and differentiation and the tightening of connections between adjacent cells [48,49]. Research indicates that the Hippo pathway plays a crucial role in modulating CM progression and heart size. The Hippo/YAP pathway is activated in cardiac disease. YAP is overexpressed in the hearts of diabetic individuals with HF [50]. Inactivating the Hippo pathway or activating its downstream effectors can improve heart regeneration [16]. Activated Yap in an adult mouse heart induces myocardial regeneration and enhances contractility following myocardial infarction [17,51]. Therefore, drugs that inhibit the Hippo pathway may be novel therapies for stimulating cardiac regeneration.

4. ECM proteins and cardiac regeneration

Lower vertebrates have amazing heart regeneration capabilities. After part of the ventricular muscle of adult zebrafish is removed, the ventricular lumen bleeds heavily within a few seconds, and a massive clot of erythrocytes forms in the wound. Gradually, erythrocytes are replaced by fibrin, and CMs start to dedifferentiate. Instead of undergoing fibrosis and scarring, cells proliferate to replace lost CMs. After several days, the removed tissue is completely replaced with functional heart tissue [6]. Interestingly, in newts and zebrafish, ECM component genes exhibit a highly responsive expression pattern following myocardial injury. During cardiac remodelling, a large amount of ECM is deposited. The accumulation of collagen and FN may be essential for myocardial reconstitution [52,53]. The neonatal mammalian heart possesses substantial regenerative potential [54]. Porrello et al. reported that the myocardium of one-day-old neonatal mice could regenerate after localized surgical resection [55]. Many researchers have focused their attention on neonatal heart regeneration. During the first two days of life, coronary ligation and apical resection injuries lead to heart regeneration in neonatal mammals [56]. The injury response of neonatal mammalian hearts begins with quick clotting, inflammatory cell infiltration to the injured site, stimulation of the epicardium, and CM proliferation. However, this strong regenerative response did not occur in mice that were injured seven days after birth [55], indicating that the regenerative potential of the heart decreases sharply shortly after birth. Cardiac fibrosis rather than regeneration occurs in the injured adult mammalian heart. The loss of CMs can eventually impair the contractility of the remaining myocardium, resulting in adverse cardiovascular events.

The ECM is dynamically remodelled after heart injury. ECM degradation and remodelling are regulated mainly by metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). MMPs are synthesized as soluble or membrane-anchored

proteinases that can degrade components of the ECM and activate cytokines and other pro-MMPs. MMP-2 and MMP-9 are involved in the degradation of sarcomeric structures under ischaemic conditions, which leads to cardiac systolic dysfunction [57]. MMP-9 is involved in the dysfunction of the remodelling process by promoting collagen deposition and degradation of the ECM [58]. In addition, disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) were shown to be significantly associated with ECM degradation and remodelling [59]. ADAMTS-1 regulates the ECM composition and activates FAK-ERK signalling [60]. ADAMTS-16 aggravates cardiac hypertrophy and fibrosis by promoting cardiac fibroblast activation, leading to remodelling and deposition of ECM proteins [61]. ADAMTS-7 binds and degrades TIMP-1, reducing the inhibitory effect of TIMP-1 on MMP-9, which subsequently influences the formation of atherosclerotic plaques [62]. ADAMTS-5, the key protease involved in the degradation of proteoglycans and versican in the heart, is linked to impaired cardiac function [63]. The activity of the MMP is tightly regulated by TIMPs at the transcriptional level and after protein translation [64]. Another type of protease involved in cardiac extracellular matrix degradation and remodelling is cathepsins. The activity of cathepsins is generally increased in the hearts of patients with cardiovascular diseases [65]. Furthermore, Hohl et al. reported that the overexpression of cathepsin A (CatA) results in a decrease in its novel substrate, the extracellular antioxidant enzyme superoxide dismutase (EC-SOD), which contributes to ECM remodelling and left ventricular remodelling [66]. Cathepsin A is also associated with ventricular remodelling and atrial cardiomyopathy [67]. Multiple enzymes work together to modulate the homeostasis of the ECM during cardiac remodelling [68]. In the early stage after heart injury, neutrophils and macrophages invade rapidly, and inflammatory mediators induce neutrophils and macrophages to produce MMPs and subsequently degrade the ECM [21]. Then, phagocytes remove dead cells and matrix debris and induce the production of anti-inflammatory mediators, marking the transition to heart repair, and the ECM is deposited and enriched [69]. However, excessive deposition of the ECM can result in fibrosis, tissue scarring, and cardiac dysfunction [70]. Thus, maintaining a delicate balance between the destruction and accumulation of ECM is crucial for cardiac repair.

The role of the ECM in the pathophysiology of cardiovascular disease is being increasingly investigated. Dilated cardiomyopathy (DCM) is a condition characterized by left ventricular dilation and thinning, coupled with systolic dysfunction. Excessive deposition of ECM components leading to fibrosis is a key feature of DCM. Animal and human studies have shown a sustained increase in type I and type III collagen synthesis and deposition [71] and an increase in the type I/type III collagen ratio in myocardial tissue [72]. Another feature of DCM is increased matrix turnover. Several MMPs are induced in DCM hearts at mRNA, protein and activity levels compared to normal tissue. The delicate balance between MMP and TIMP is important for myocardial remodelling [73,74]. Analysis of the GEO dataset revealed a number of genes that were differentially expressed between the DCM and control groups, with most of the upregulated genes being glycoproteins and most of the downregulated genes being secreted factors [74]. In addition to these well-established components of the ECM, many less studied ECM proteins are beginning to receive attention for their role in CVD. Studies have implicated proteins such as tenascin-C, biglycan, versican and lumican in the regulation of myocardial remodelling in

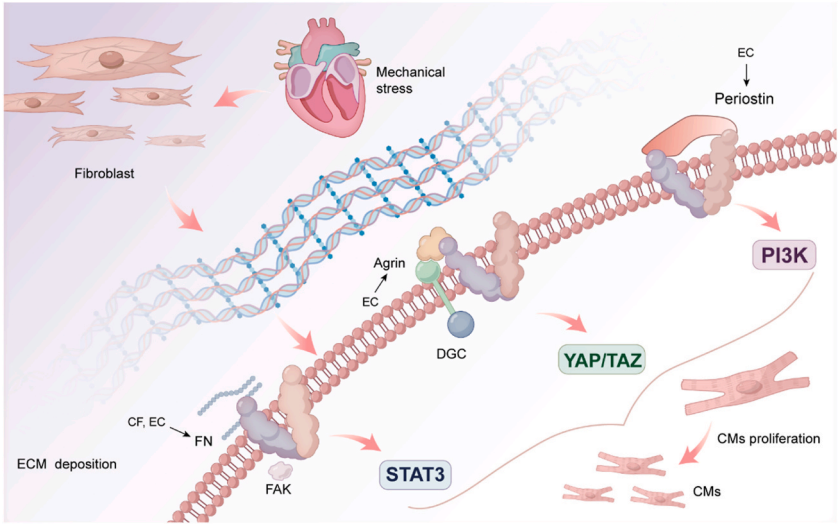

Fig. 2. The ECM during cardiac regeneration.
Mechanical stress activates the matrix-preserving fibroblast phenotype and induces the production of MMPs and TIMPs, which cause ECM remodelling. The alteration of ECM components modulates the proliferation and differentiation of CMs, among which FN, agrin and periostin are three important bioactive factors that regulate cardiac regeneration. FN is mainly secreted as a soluble protein by different cell types, such as CFs and endothelial cells (ECs), and is deposited after heart injury. It can regulate CM proliferation, which is mediated by β1 integrin. Agrin is a large matrix proteoglycan that is mainly secreted by ECs and acts as a ligand for a variety of receptors. In vivo and in vitro, the addition of agrin promotes the growth and differentiation of CMs through Yap-DGC-mediated signalling. Periostin is absent in healthy myocardium, and pathological injury stimulates the production and secretion of periostin through activated fibroblasts. In an adult mouse model of MI, exogenous expression of periostin has been shown to augment myocardial development following injury and facilitate the process of cardiac repair, thereby improving ventricular remodelling and function.

response to injury [75–79]. Notably, lumican has been shown to be upregulated in myocardial fibrosis and is associated with the progression of hypertrophic cardiomyopathy [80]. The lesser-known ECM proteins represent an emerging frontier in the study of cardiovascular disease, offering new avenues for understanding myocardial remodelling and potential therapeutic targets.

A comparison of the global transcriptomes between potentially regenerative and nonregenerative hearts revealed that the highest number of differentially expressed transcripts encode components of the ECM and structural components of the cytoskeleton. The composition of the ECM is different and includes elastin, collagen, and laminin. Zebrafish ECM can restore ischaemic myocardial function in adult mouse CMs and induce cardiac regeneration. In vitro, the zebrafish ECM has been shown to exert chemotactic and proliferative effects on populations of human cardiac progenitor cells [81]. Treatment with neonatal cardiac ECM restricts the expansion of the left ventricular scar following myocardial infarction in adult mammals and promotes revascularization of the injured region, leading to significant improvements in cardiac function [82]. LC–MS/MS can be used to measure modifications in the structure of the ECM in the foetus to the adult. As the heart develops, the levels of collagen I, collagen III, and laminin progressively increase. Conversely, FN and periostin levels decrease with age [83]. These data suggest that ECM constituents change throughout development and may modulate the regeneration ability of CMs. The major ECM components associated with cardiac regeneration are shown in Fig. 2.

4.1. Fibronectin (FN)

FN is a multidomain glycoprotein that is composed of two subunits, each of which is approximately 250 kDa in size [84]. FN is expressed during mesoderm induction and fetal cardiac development, and is reduced after birth [85]. FN plays an essential role in promoting cardiac differentiation of human pluripotent stem cells [86]. FN expression is correlated with cardiac repair following MI in adult mice [87,88]. FN stimulates protection and progression through the β1 integrin-FAK-STAT3 pathway [87]. Another study showed that FN is essential for heart regeneration in zebrafish. The epicardium is enriched in FN at the injury site following cardiac impairment. With the accumulation of FN, itgb3 is overexpressed in CMs to promote regenerative responses [89]. Although FN produced by embryonic cardiac fibroblasts can stimulate the progression of cultured mammalian CMs [90], there is no evidence that FN is directly involved in the proliferation of CMs during cardiac regeneration [89].

4.2. Agrin

Agrin is a principal extracellular heparan sulfate PG that is enriched in the neonatal heart but not in adults. Agrin delays the maturation of CMs in newborns, and it is necessary for heart regeneration after surgical resection during the first day after birth. In vitro administration of agrin stimulates CM proliferation. Furthermore, agrin treatment improved heart function and induced heart regeneration after myocardial infarction (MI) in adult mice. The molecular mechanism involves the binding of agrin to the dystrophin-glycoprotein complex (DGC) via dystroglycan 1 (Dag1), facilitating its disassembly, which subsequently leads to myofibril disassembly and Yap translocation [91]. The Yap-DGC complex is closely related to CM proliferation [92]. MMP14 has a positive effect on agrin accumulation in neonatal mice to regulate cardiac regeneration [93]. In addition to increasing the proliferation of CMs, agrin exerts pleiotropic effects, such as inhibiting fibrosis, regulating the immune response and angiogenesis, and collectively strengthening heart repair [94].

4.3. Periostin

Periostin is a constituent of the ECM that contains a signal peptide and four fasciclin-1 domains and is overexpressed during foetal cardiac development and in neonatal hearts. Periostin induces the re-entry of differentiated mononucleated CMs into the cell cycle via integrins and the phosphatidylinositol-3-OH kinase (PI3K) pathway. Following MI in adult rats, periostin promotes the progression of CMs and enhances cardiac function [95]. However, another study suggested that, while periostin is stimulated in the heart after injury, it does not influence myocyte composition, cell cycle activity, or cardiac repair [96]. The suppression of postinfarction myocardial regeneration in newborn mice due to the absence of periostin is attributed to the inhibition of the PI3K/GSK3β/cyclin D1 signalling pathway [97]. Overall, these findings indicate that periostin is essential for cardiac regeneration.

4.4. Epicardium

The epicardium, the outermost protective layer of the adult heart, can be activated after injury and undergo epithelial–mesenchymal transition (EMT) to generate epicardium-derived progenitor cells (EpiPCs). Epicardial cells contribute to postinjury repair and regeneration [98,99]. On the one hand, EpiPCs are multipotent cardiac progenitors that can differentiate into various cardiac cell types [100]. Concurrently, following EMT, epicardial cells also secrete paracrine factors that support cardiac repair and aid in regeneration [101,102]. Notably, some hormones, such as oxytocin, lead to significant epicardial EMT and the migration of EpiPCs to support regeneration [103].

In addition, other types of ECM components are involved in cardiac regeneration. Versican, a fibroblast-derived ECM protein, promotes cardiomyocyte proliferation and cardiac repair by activating integrin β1 and downstream signalling molecules [78]. Embryonic ECM proteins such as SLIT2 and NPNT create a favourable environment that facilitates postnatal cardiomyocyte cytokinesis [104]. Collagen V regulates scar size in an integrin-dependent manner by modulating the mechanical properties of scar tissue and is a key driver of cardiac function after injury [105]. Crosstalk between cardiomyocytes and the ECM is critical to cardiac repair and

regeneration, and an increasing number of studies are focusing on this area, which holds great promise for the development of cardiac regenerative medicine [106,107].

5. ECM stiffness and cardiac regeneration

In addition to its biochemical composition, the mechanical characteristics of the ECM play a decisive role in heart regeneration. The loss of regenerative potential in neonatal mouse hearts coincides with a rapid increase in stiffness in the heart microenvironment [108]. One-day-old neonatal mice exhibit strong regenerative capacity following heart amputation, and this capacity sharply declines within 48 h [108]. The mechanical characteristics of cardiac ECM were measured by atomic force microscopy, and the hardness of the P2 heart was 50 % greater than that of the P1 heart. Reducing the stiffness of the ECM with a pharmacological suppressor restored cardiac regeneration competence [108]. This observation underscores the essential role of the stiffness of the local microenvironment in determining the regenerative ability of the heart.

The stiffness of the cardiac microenvironment changes throughout progression and/or in heart disorders. The elastic modulus of the left ventricle of developing mouse hearts increases significantly at birth (12–39 kPa) [109]. In most cardiac pathological conditions, the adult heart primarily replaces damaged CMs with a collagen-rich scar. This fibrotic response further increases the stiffness of the ECM and impairs cardiac systolic and diastolic dysfunction. Following ligation of the left anterior descending coronary artery, the elastic modulus of the infarct region in rats was increased threefold compared to normal rats (18–55 kPa) [110]. Neonatal CMs from rats and mice grown on rigid matrix stopped dividing, and myofibrillar organization increased. In contrast, compliant matrices promoted dedifferentiation, proliferation, and clonal expansion of heart cells. These findings suggest that ECM stiffness regulates the ability of CMs to divide and mature [111]. A decrease in heart stiffness induced by β-aminopropionitrile in a mouse MI model could enhance the protective effect of foetal dECM on cardiac function and induce heart regeneration, as indicated by increased angiogenesis, reduced fibrosis, and fibroblast activation [112,113]. Overall, alterations in the microenvironment of the heart significantly affect the regenerative response.

Non-coding RNAs (ncRNAs) are functional RNA molecules that do not encode proteins. Recent studies have shown that ncRNAs, such as microRNAs (miRNAs) and long non-codingnoncoding RNAs (lncRNAs), engage in modulating ECM stiffness and cardiac regeneration [114]. MiRNAs are small ncRNAs with a length of approximately 22 nucleotides that are involved in post-transcriptional gene expression regulation. These molecules silence and regulate gene expression by interacting with complementary mRNA sequences [115]. MiRNAs regulate the expression of ECM genes, and changes in ECM components determine their stiffness, which consequently affects miRNA expression. MiR-17 expression is upregulated in the myocardium post-MI, which accelerates matrix degradation and ventricular dilation. Inhibition of miR-17 can reduce excessive post-MI MMP activity and improve cardiac function [116]. Studies have also shown that ECM stiffness affects myocardial fibrosis by regulating miRNAs. For example, miR-21, miR-433, miR-503, miR-34a, and miR-155 play roles in promoting fibrosis, whereas miR-26a, miR133a, miR-19a/b-3p, miR-29b, miR-22, and miR-let-7i play antifibrotic roles [117]. LncRNAs are a class of functional RNA molecules that are greater than 200 nucleotides in length. LncRNAs, such as n379599, n379519, n380433, n384640, and n410105, are used as enhancers of genes encoding ECM proteins to regulate the expression of ECM genes [118]. Moreover, lncRNAs contribute to the deposition of ECM components by binding to specific ECM proteins [114]. In turn, the stiffness of the ECM also regulates the expression of specific lncRNAs [119]. Another mechanism by which lncRNAs regulate the ECM is by acting as endogenous sponges for miRNAs, such as the lncRNA/miRNA axis of RP11-820/miR-3178, CASC2/miR-133b, and MIAT/miR-29a-3p [120–122]. In general, ncRNAs are important regulatory factors of ECM stiffness and cardiac regeneration.

6. Clinical applications

The clinical application of ECM-based biomaterials, such as patches and injectable hydrogels, in heart regeneration and repair is a rapidly developing field. These biomaterials offer multiple advantages due to their inherent 3D structure. They can provide biomechanical support, function as substrates for cell differentiation and migration, can be used to deliver a series of bioactive compounds, and can reduce the risk of infection.

6.1. Patches

Tissue-engineered patches made with ECM-based materials have shown promise in guiding tissue formation and improving mechanical and electrical functions in the heart [123]. Grafting an acellular 3D collagen type I patch onto the impaired myocardium induces neoangiogenesis and reduces left ventricular remodelling [124]. ECM patches originating from the small intestinal submucosa (SIS) have also been widely used in cardiovascular surgery as scaffolds for tissue repair [125–128]. Other biomaterials, such as microcollagen/PLGA bimodal fibrous patches and chitosan/silk fibroin-modified nanofibrous patches, have also shown promising effects by providing a mechanical scaffold to prevent adverse ventricular remodelling and establish a beneficial microenvironment to increase the proliferation and retention of engrafted stem cells [129,130]. Although cardiac patches are an effective way to deliver therapeutics to the heart, the implementation of most cardiac patches requires open-chest surgery and is difficult to perform.

6.2. Injectable hydrogels

Injectable hydrogels include naturally derived and synthetic materials. Given their high moisture content, biocompatibility, and

easy adjustment, injectable hydrogels have become among the most promising biomaterials. Naturally-derived injectable hydrogels, including collagen, fibrin, hyaluronic acid, and gelatine, have been investigated for their regenerative potential [131]. Synthetic materials offer advantages in terms of adjustable mechanical and functional properties. Decellularized ventricular ECM hydrogels and degradable elastin-like recombinase-based hydrogels have been shown to increase the number of endogenous myocardial cells, reduce fibrosis, and promote functional recovery after myocardial infarction [132–134]. Intramyocardial injections of degradable elastin-like recombinamer-based hydrogels result in less fibrosis and marked functional recovery after nontransmural myocardial infarction [135]. Moreover, hyaluronic acid hydrogels loaded with stem cells have been shown to promote heart regeneration [136–138]. The use of recombinant human collagen III thermoresponsive hydrogels, which improve cardiac function, reduce scar size and inflammation, and increase vascularization, has also been explored [139,140]. Early injection of collagen hydrogels is a promising therapy for the treatment of heart infarction, especially when it is administered soon after the onset of ischaemia and inflammation [140]. Moreover, the combination of conductive hydrogel patches and injectable hydrogels has resulted in pronounced increases in cardiac function [141]. Nevertheless, there are still obstacles that must be addressed in the optimal use of hydrogels for heart treatment. Factors such as the polymer concentration, stiffness, spatial placement, and injection timing need to be extensively examined and optimized. We summarize the characteristics and clinical uses of ECM-based biomaterials in Table 2. Future research is needed to determine the most effective strategies and overcome limitations in the clinical application of these biomaterials.

Currently, several epicardial patches and injectable hydrogels/scaffolds are in the preclinical and clinical trial stages. A randomized clinical study (NCT04011059) is ongoing to evaluate the safety and efficacy of coronary revascularization surgery with the injection of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) and the placement of epicardial extracellular matrix patches. VentriGel, an extracellular matrix hydrogel derived from decellularized porcine myocardium, has advanced to Phase I clinical trials (NCT02305602). The transendocardial injection of VentriGel for the treatment of left ventricular dysfunction following myocardial infarction has been confirmed to be both safe and feasible [142]. Results indicate that VentriGel therapy can improve left ventricular remodelling in patients with myocardial infarction for more than one year [142]. The clinical feasibility, safety, and physiological effects of CorMatrix-ECM bioscaffold therapy in human patients were evaluated in a non-randomized, open-label preclinical trial (NCT02887768). The CorMatrix-ECM bioscaffold provides an appropriate microenvironment that enhances perfusion in infarcted myocardium and reduces myocardial scar burden [143]. Additionally, injectable hydrogels based on calcium alginate (NCT01311791, NCT00847964) and calcium gluconate (NCT01226563) have undergone clinical trials to assess their safety and feasibility. Intramuscular biomaterial injection therapy, which has completed numerous clinical trials since its introduction, offers a promising

Table 2
ECM-based biomaterials for cardiac tissue engineering.

Type	Composition	Species	Disease model	Function	Reference
patch	collagen type I	Fischer 344 (F344) rats	MI	induce neo-angiogenesis reduce cardiac remodelling	[124]
patch	SIS-ECM	Landrace pigs	IR	promote vasculogenesis enhance myocardial repair and functional recovery	[128]
patch	collagen and poly (D,L-lactic-co-glycolicacid)(Col/PLGA)	New Zealand White rabbits	MI	improve cytocompatibility and proliferation capacity long term stem cells retention capability attenuate cardiac remodelling	[129]
patch	chitosan/silk fibroin	Sprague Dawley rats	MI	promote neovascularization inhibit cardiac fibrosis and apoptosis	[130]
hydrogel	decellularized ventricular ECM	Sprague-Dawley rats Yucatan mini pig	IR	increase endogenous CMs in the infarct area maintain cardiac function	[132]
hydrogel	elastin	Sheep	MI	enhance angiogenesis limit fibrosis improve cardiac function	[133]
hydrogel	hyaluronate and hESC-CMs	Sprague Dawley rats	MI	improve cardiac functional recovery delay left ventricular remodelling prevent arrhythmias	[136]
hydrogel	hyaluronic acid loaded with hMSCs	Sprague Dawley rats	MI	promote angiogenesis inhibit inflammatory response	[137]
hydrogel	collagen type Ill	Mice	MI	increase vascularization reduce scar size and inflammation improve cardiac function	[139]
hydrogel	collagen matrix	Mice	MI	alter the myocardial cytokine profile promote angiogenesis reduce fibrosis and cell death	[140]
coadministration of patch and hydrogel	dopamine-conjugated gelatin and dopamine-modified polypyrrole	Sprague Dawley rats	MI	promote angiogenesis provide mechanical support	[141]

treatment option to reduce left ventricular remodelling and improve cardiac function in patients with cardiac injury.

7. Conclusion and perspective

Heart regeneration is still a significant factor in the context of cardiovascular research. The ECM has been recognized as a pivotal component in heart formation and regeneration. Its dynamic remodelling following cardiac injury and impact on intercellular signalling have been recognized as central factors in the repair process. Determining the interactions between cells and the ECM will yield significant insights into the pathophysiology of heart disease.

By providing a combination of biomolecular and biophysical cues, ECM-based biomaterials hold great promise for facilitating cardiac repair and regeneration. Although preclinical research has shown encouraging outcomes, the clinical application of ECM-based biomaterials is still in its early stages. There are still significant challenges in clinical translation. First, biological variability and batch-to-batch differences have potential effects on clinical efficacy. The variation can be mitigated by maintaining stricter production conditions and single batch processing. Although ECM-based biomaterials generally have excellent biocompatibility, they can still trigger adverse immune responses after implantation. The addition of immunosuppressive molecules is beneficial for improving biocompatibility. By improving the reproducibility and long-term viability of these materials through optimal mechanical, degradation, and biological activities, these strategies could lead to a new era of heart regeneration. In general, cardiac regeneration is a fascinating biological phenomenon, and stimulating human heart regeneration is our shared goal.

CRediT authorship contribution statement

Xiying Wang: Writing – original draft. **Shuo Yu:** Writing – review & editing. **Lan Xie:** Investigation. **Meixiang Xiang:** Writing – review & editing. **Hong Ma:** Writing – review & editing.

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Data availability statement

No data was used for the research described in the article. This review article has not been deposited in publicly available repository.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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