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Insights into the key roles of epigenetics in matrix macromolecules-associated wound healing

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Abbreviations: ADAMs, a disintegrin and metalloproteinases; ADAMTS, ADAMs with thrombospondin motifs; Col, collagen; CS, chondroitin sulfate; CTGF, connective tissue growth factor; DS, dermatan sulfate; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transition; FGF, fibroblast growth factor; GAG, glycosaminoglycan; HA, hyaluronan; HAS, hyaluronan synthase; HPSE, heparanase; HS, heparan sulfate; HSPG, heparan sulfate proteoglycan; IL, interleukin; KS, keratan sulfate; LAM, laminin; miR, microRNA; MMP, metalloproteinase; ncRNAs, non-coding RNAs; NDST1, N-deacetylase/N-sulfotransferase-1; NF-κB, nuclear factor-κB; PDGF, platelet-derived growth factor; PG, proteoglycan; pri-miRNA, primary microRNA; RISC, RNA-induced silencing complex; SLRPs, small leucine rich proteoglycans; αSMA, alpha smooth muscle actin; TGF-β, transforming growth factor β; TIMP, tissue inhibitor of metalloproteinase; TLRs, toll-like receptors; TNF-α, tumor necrosis factor α; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator; UTR, untranslated region; VEGF, vascular endothelial growth factor

Abstract

Extracellular matrix (ECM) is a dynamic network of macromolecules, playing a regulatory role in cell functions, tissue regeneration and remodeling. Wound healing is a tissue repair process necessary for the maintenance of the functionality of tissues and organs. This highly orchestrated process is divided into four temporally overlapping phases, including hemostasis, inflammation, proliferation and tissue remodeling. The dynamic interplay between ECM and resident cells exerts its critical role in many aspects of wound healing, including cell proliferation, migration, differentiation, survival, matrix degradation and biosynthesis. Several epigenetic regulatory factors, such as the endogenous non-coding microRNAs (miRNAs), are the drivers of the wound healing response. microRNAs have pivotal roles in regulating ECM composition during wound healing and dermal regeneration.Their expression is associated with the distinct phases of wound healing, and they serveas target biomarkers and targets for systematic regulation of wound repair. In this article we critically present the importance of epigenetics with particular emphasis on miRNAs regulating ECM components (i.e. glycoproteins, proteoglycans and matrix proteases) that are key players in wound healing. The clinical relevance of miRNA targeting as well as the delivery strategies designed for clinical applications are also presented and discussed.

Extracellular matrix: a dynamic regulatory network

Extracellular matrix (ECM) is the non-cellular highly organized three-dimensional meshwork that is formed by a variety of interconnected matrix macromolecules ECM vigorously interacts with cells to control cellular phenotype and properties [1, 2]. Collagens, fibronectin, elastin, laminins, proteoglycans (PGs), hyaluronan (HA), glycoproteins and matricellular proteins are among the major ECM components. Two subtypes of ECM named interstitial and pericellular ECMs can be distinguished in regard to their localization and structure. Interstitial matrix encompasses cells, whereas pericellular matrix encircles cells in close contact, supporting their anchorage. Interstitial matrix is dominated by fibrillar collagens, such as collagen I and III, PGs, HA and several matrix glycoproteins [1, 2]. An example of pericellular matrix is the basement membrane that underlies epithelial cells, which provides many binding sites to mediate their strong docking. It is enriched in collagen IV and laminins, which that form two distinct interconnected networks by several molecular linkers, such as perlecan, a pericellular PG.

All ECM constituents are produced by several cells resting within this scaffold, such as fibroblasts, epithelial, endothelial and immune cells, and their composition and fine structure differs in different types of ECM and between tissues. ECMs with different composition of matrix molecules can vary in regard to overall structure, matrix mechanical properties, stiffness and viscoelasticity providing tissues with distinct functionality [3]. Furthermore, ECM components like PGs are able to bind and store growth factors and other bioactive molecules creating a reservoir of such molecules within the ECM [3]. Resting cells interact with ECM molecules via binding through specific cell surface receptors such as integrins, cell-surface PGs, syndecans and glypicans, discoidin domain receptors (DDRs) and the HA receptor CD44, which binds a large variety of matrix components [2, 4-6]. By these interactions, matrix-embedded cells integrate mechanical and chemical signals that control cell fate and functions, such as cell phenotype, synthesis of matrix microenvironment, cell proliferation, migration, invasion and survival [7]. ECM composition and structure is crucial for tissue homeostasis, whereas active ECM remodeling occurs under physiological and pathological conditions. ECM degradation is a crucial process in tissue remodeling. A huge variety of degrading enzymes is involved in matrix breakdown, such as matrix metalloproteinases (MMPs), a disintegrin and metalloproteinases (ADAMs), ADAMs with thrombospondin motifs (ADAMTs), cathepsins, plasminogen activators, and glycosaminoglycan (GAG) degrading enzymes like hyaluronidases and heparanase (HPSE) that cleave HA and heparan sulfate (HS) chains, respectively [8-11]. These enzymes not only actively degrade matrix during remodeling by creating space for new ECM formation by resident cells, they also liberate bioactive molecules, such as growth factors stored within ECM as well as proteolytic fragments of matrix molecules named

matrikines [8, 12, 13]. In turn, these molecules could bind to cell surface receptors on resident cells and regulate their functions and matrix remodeling. Accumulating data on the dynamic interplay between ECM and resident cells confirm its critical role in wound healing [1, 2, 8, 13]. For example, recessive dystrophic epidermolysis bullosa caused by mutations in the collagen VII α1 chain is associated with dysregulated wound healing. Collagen VII is responsible for the anchorage of the epidermis to the underlying dermis and patients with this disease suffer from blistering and chronic wounds leading to fibrosis and are prone to develop squamous cell carcinoma [14]. In another example, defective epithelial basement membrane regeneration after injury associated with abnormal deposition of laminin and nidogen is related to corneal fibrosis [15]. Abnormal expression of cell surface PGs such as syndecans is also associated with irregular wound healing in animal models. Mice lacking syndecans exhibit decreased pro-fibrotic signaling, affected wound healing and increased cardiac rupture upon infarction demonstrating a key role for these PGs in tissue repair [16].

Wound healing phases and the involvement of extracellular matrix

Wound healing is an essential and highly orchestrated process, necessary to keep the integrity and functionality of tissues and organs [8,13,14]. In this well-regulated dynamic process, several cell types that cooperate with ECM components in a time- and context-dependent manner contribute to re-establish the wounded tissue. This dynamic reciprocity between cells and ECM plays a crucial role in many aspects of healing [14]. Although most wounds heal nearly properly and tissues regain the pro-wound functionality, abnormal wound healing occurs, resulting in non-healing wounds and the development of chronic wounds, or in excessive wound healing and fibrosis. The development of chronic wounds is often associated with other comorbidities, such as diabetes and aging. On the other hand, excessive healing leads to fibrosis and development of hypertrophic scars and keloids in skin [13-15].

Wound healing is parsed into four temporally overlapping stages, named hemostatic, inflammatory, proliferation and remodeling phases, which occur at different rates across the wound (Figure 1). Immediately after tissue injury, the hemostatic phase begins and the coagulation cascade is activated to seal the breach and impede infection. This phase is followed by the inflammatory phase where the activation of the coagulation cascade induces the production of cytokines and growth factors and the recruitment of inflammatory cells. Inflammation induces the migration and proliferation of stromal cells within the wound bed, the formation of granulation tissue and neovascularization during the proliferation phase. Contraction of newly formed ECM by myofibroblasts and re-epithelialization occurs

at this phase to restore tissue integrity and reduce wound size. Finally, the remodeling phase is characterized by a decrease in the overall number of cells and vessels within wounded bed and the replacement of newly produced matrix with a mature ECM with proper mechanical properties.

The hemostatic phase initiates the coagulation cascade to seal the rupture. Particularly, once the tissue is damaged, the initiation of coagulation cascade starts and platelets accumulate in a provisional matrix composed of fibrinogen, fibrin, fibronectin and vitronectin. Fibrinogen is a plasma glycoprotein that is cleaved by α-thrombin to fibrin monomers that spontaneously form insoluble fibrin polymers. They are subsequently cross-linked by factor XIIIα to create a more stable clot that stems blood loss and provides a platform for tissue repair [13,14]. Factor XIIIα also facilitates the incorporation of soluble fibronectin into the fibrin network. Both fibrin/fibrinogen and fibronectin as well as vitronectin are capable of interacting with platelets, immune cells, fibroblasts, endothelial cells, keratinocytes via cell surface receptors such as integrins and cell surface PGs regulating cell signaling, adhesion, migration, proliferation and differentiation [7, 17-19]. In addition, they bind growth factors, such as platelet derived growth factor (PDGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), vascular growth factor (VEGF), thus providing a milieu that can control cell fate and functions [17]. During this phase, HA accumulates in early granulation tissue Through binding to fibrinogen, it realigns the fibrin matrix causing it to swell and rendering it more porous, thus facilitating cell migration [20] (Figure 1). The next step, the inflammatory phase, is characterized by recruitment of immune cells into the wounded area and it is followed by the subsequent proliferation phase where damaged tissue is replaced. In the inflammatory phase, approximately a day post wounding, leukocytes migrate into the wound site and the fibrin-rich provisional matrix, attracted by platelet-released PDGF and TGF-β [17]. HSPGs on endothelial cells facilitate the infiltration of leukocytes into wound areas [21]. Neutrophils and macrophages serve to limit infection and to remove cell debris and foreign material through phagocytosis. Leukocytes release proteases to degrade ECM such as neutrophil elastase that break down molecules suppressing angiogenesis, and MMPs that degrade several matrix components, such as collagen I, thereby facilitating cell migration [22-25]. Furthermore, they release matrix-stored growth factors and cytokines as well as matrikines able to regulate multiple cell functions during the inflammatory process. Matrix PGs such as decorin and lumican that suppress growth factor induced signaling are also displaced in this phase [5]. Infiltrating immune cells secrete several inflammatory mediators and growth factors such as PDGF, epidermal growth factor (EGF) and TGF-β to promote further the recruitment of inflammatory cells and to attract stromal cells to the wound bed [17] (Figure 1). In the proliferation phase, inflammation starts to decrease two to three days post wounding and

stromal cells migrate into the wound area, attracted by growth factors such as FGF secreted by inflammatory cells. There, migrated fibroblasts prime the matrix for immigration and proliferation of various cellular components under the control of growth factors such as TGF-β released by platelets and leukocytes [17]. TGF-β triggers fibroblasts to create a provisional ECM enriched in fibronectin, matricellular proteins such as tenascin and thrombospondin, entactin, collagen and PG with both adhesive and anti-adhesive properties that promotes the migration of endothelial and epithelial cells, keratinocytes and fibroblasts [19, 26-28]. The new matrix production is accompanied by decreased synthesis of MMPs and initiation of epithelial cell migration under the control of EGF and TGF-α produced by platelets, leukocytes and keratinocytes [29]. As the fibroblasts immigrate and settle in the wound bed, they start to produce a fibrous ECM enriched in fibrillar collagen III and I, and non-fibrillar collagen IV, VI and VII that interconnect ECM molecules with fibrillar collagens [13, 17]. Fibronectin acts as scaffold for collagen deposition and PGs such as decorin and lumican, which are re-expressed at this stage, contribute to fibrillar collagen organization creating a collagen-rich matrix that replaces fibrin-rich matrix [5, 13, 30, 31]. The small leucine rich PGs (SLRPs) decorin and lumican also limit cell signaling by suppressing the activation of numerous growth factor receptors, and by directly binding and blocking growth factors to reduce excessive cell proliferation and migration [5]. Fibrillar collagens are responsible to provide new matrix with tensile strength, whereas collagen IV is important for attachment of ECM to vasculature. In skin, keratinocytes migrate to re-epithelialize the wound are and contact-inhibited keratinocytes behind the leading edge participate in the production of laminins and collagen IV that reconstitute the basement membrane where they are strongly anchored by hemidesmosomes [13]. Finally, the remodeling phase is responsible for wound resolution and restoration of proper functional tissue (Figure 1). The aim of this phase that may last up to one or more years is to replace the wounded tissue with scar tissue that will be covered by new epithelium. During this phase, the granular tissue is replaced by mature ECM. The provisional supportive ECM enriched in matricellular proteins and collagen III is substituted by a collagen I-rich matrix with SLRPs playing a role in mature fibril formation [5, 32]. A continuous collagen synthesis and degradation occurs and collagen fibers realign, cross-linked and increase in diameter to form mature and well-organized fibers with increased tensile strength. Stromal cells are triggered by the stiffer matrix and TGF-β to adopt a myofibroblast phenotype. In turn, these cells produce more collagen and induce wound contraction [33, 34]. At the same time, apoptosis of excess cell populations increases, that is accompanied by completion of new vessel formation. The end of the wound healing process results in a scar tissue with overly aligned collagen fibers that regain almost 80% of the original tissue strength and functionality [13].

Extracellular matrix components and their roles in would healing

Proteins/glycoproteins

The collagen superfamily consists of 28 different collagen types with collagen type I and III being the two major types found in all interstitial ECMs [2]. Although collagen fibers provide appropriate strength in wounded tissue, the excessive production of tight collagen bundles is a factor that contributes to the development of hypertrophic scars [32]. It has been shown that the mechanical properties of the ECM regulate functional properties of fibroblasts including biosynthesis of ECM components, expression of MMPs as well as their differentiation to myofibroblasts even independently of TGF-β signaling [35-38]. The expression of different amounts and types of collagens during wound healing is critical. Apart from determining matrix stiffness, collagens regulate fibroblast functions relevant to wound repair. It has been shown that collagen III regulates collagen I synthesis, and a higher ratio of collagen III to collagen I is associated with scarless fetal wound healing in various models, whereas its absence promotes myofibroblast differentiation and scar formation [32, 39, 40]. Similarly, the absence of collagen V results in abnormal collagen I fibril formation since it is required for proper collagen fibrillogenesis and functional matrix deposition [41, 42]. Another collagen that is involved in tissue repair is collagen VI that is detected in wounds three days post wounding up to months and inhibits the apoptosis of fibroblasts via downregulation of Bax [43]. Collagen VII plays a dual role in wound healing It facilitates the migration of fibroblasts and regulates the expression of cytokines in macrophages [44]. Furthermore, collagen VII is required for re-epithelialization through organization of laminin-332 at the dermal-epidermal junction, which in turn promotes the polarized expression of α6β4 integrin in basal keratinocytes, thus promoting laminin-332/ α6β4 integrin signaling that guides keratinocyte migration [44]. Exogenous addition of collagen VII into skin wounds decreased the expression of fibrogenic TGF-β2 and increased the expression of anti-fibrogenic TGF-β3, resulting in less collagen deposition and prevention of fibrosis [45]. Furthermore, patients with recessive dystrophic epidermolysis bullosa caused by mutations that affect the amount or/and the function of collagen VII are characterized by chronic non-healing wounds, persistent inflammation, increased TGF-β signaling, elevated number of myofibroblasts and development of fibrosis [14].

Fibronectin is another ubiquitous component of ECM in the wound bed. It is a glycoprotein consisting of two subunits covalently connected with disulfide bonds at their C-termini. Each subunit consists of three repeating modules termed type I, type II and type III. Monomers are comprised of twelve type I repeats, two type II repeats and 15-17 type III repeats [2, 19]. Due to alternative splicing, fibronectin can exist in

multiple variants that can be found in soluble form in plasma or in an insoluble cellular form in the ECM. Cellular fibronectin contains two extra type III repeats named extra domain A (EDA) and extra domain B (EDB) [19]. Fibronectin is assembled into supermolecular fibers that are interconnected by intermolecular non-covalent bonds forming an extended network. Cells produce new fibronectin molecules to fibronectin fibers that are incorporated and grow the network. Alternatively, cells can assemble soluble plasma fibronectin into insoluble fibers in the wound. Fibronectin is covalently connected to fibrin fibers and factor XIII further stabilizes this interaction [2, 19, 32]. Fibronectin entrapped within the provisional fibrin-rich matrix undergoes conformational changes that expose (Arg-Gly-Asp) RGD cell binding sites for $\alpha v\beta 3$ integrins on fibroblasts, thus promoting their migration into the wound [32]. Furthermore, fibronectin possess many binding sites for cells and other ECM components, creating a provisional matrix that controls cellular properties and matrix deposition. It has been shown that a fibronectin matrix is required for deposition of collagen I and III and other matrix components such as fibrillin, tenascin-C, fibulin and latent TGF-β binding protein [46-53]. In addition, it controls covalent cross-linking of fibrillar collagens and elastin by regulating the proteolytic activation of lysyl oxidase [54]. Fibronectin matrix fibers can also bind growth factors, such as PDGF, VEGF, FGF, TGF-β members creating a matrix reservoir for these molecules. They can penetrate and bind to fibronectin fibers, protected from proteolytic degradation and creating a stable concentration gradient within the ECM. They may be liberated upon ECM degradation or may be available to interact with cell surface receptors upon cell binding to fibronectin fibers, thus triggering signaling in neighboring or adherent cells [19]. Fibronectin accumulation is also associated with abnormal wound healing and fibrosis. Expression of a fibronectin splice variant containing EDA (Fn-EDA) is increased during wound healing and its level is decreased as myofibroblasts synthesize collagen I-rich matrix and declines almost completely in adult tissues [17, 55]. Fn-EDA is abundant in keloids and it has been associated with altered integrin binding and development of fibrosis [26, 56]. Fn-EDA is susceptible to mechanical forces that cause conformational changes to destabilize the RGD and Pro-His-Ser-Arg-Asn (PHSRN) binding sites, resulting in an integrin binding "switch". Binding of $\alpha 5\beta 1$, $\alpha 3\beta 1$ integrins to fibronectin depends on fibronectin conformation and is correlated with wound repair, whereas binding of αv integrins is independent of fibronectin conformation and is associated with abnormal wound healing and fibrosis [17]. Fibroblasts bind to Fn-EDA via $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrin to promote fibronectin and collagen deposition, a contractile phenotype and fibrosis [57, 58]. The role of Fn-EDA in normal and pathologic wound healing has been demonstrated in Fn-EDA$^{-/-}$ mice that show a lack of scar formation and re-epithelialization [59]. In

addition, toll-like receptor 4 (TLR4) binds Fn-EDA, triggering TGF-β production and establishment of a vicious cycle of fibrosis [56, 60, 61].

Vitronectin is another important ECM molecule related to wound healing. It acts in co-operation with fibronectin regulating fibroblastmigration and contraction. In order to contract a wound with full force, fibroblasts require to attach sequentially to fibronectin, vitronectin and collagen [62]. In addition, vitronectin controls the proliferative and migratory effect of fibronectin on fibroblasts by inducing conformational alterations on fibronectin fibrils and concealing RGD sequences. This reduces binding of αvβ3 integrins on fibroblasts and balances their fibronectin-induced proliferation and migration , exerting a pro-fibrotic effect in early phases of wound healing [32, 63].

Elastin fibers provide resilience and elasticity to tissues, which undergo repeated stretching and are intertwined with the rigid collagen fibers. Several proteolytic enzymes degrade elastin and liberate elastin-derived peptides that promote keratinocyte migration, an angiogenic endothelial cell angiogenic , fibroblast proliferation, induction of MMP expression and deposition of collagen I and tropoelastin [64]. Laminins (LAMs) are major components of basement membranes and are large cross-shaped heterotrimeric glycoproteins. Each heterotrimer consists of one α, one β and one γ chain. Five α (*LAMA1-5*), three β (*LAMB1-3*) and three γ chains (*LAMC1-3*) encoded by individual genes have been identified. Two isoforms of the *LAMA3* gene produce a short α3A and a longer α3B form. Laminins are named according to their chain composition. For example laminin 332 consists of the α3, β3 and γ3 chain [2, 65]. Laminin molecules self-assemble into higher order networks and interact with other ECM molecules and cell surface receptors to organize basement membrane structure and to facilitate cell adhesion and migration. Laminins are involved in re-epithelialization and angiogenesis during wound repair [2, 65]. The major laminin in epithelial tissues is laminin α3Aβ3γ2 (LM3A32 or LM332), whereas minor amounts of other laminins such as LM511, LM3A11, and LM3B32 are also present [65]. LM332 is first expressed by keratinocytes in the wound bed, followed by the expression of other basement membrane molecules, including LM511/LM521, collagen IV and VII [65-68]. Keratinocytes interact with LM332 through α6β4 integrin in the intermediate filament associated hemidesmosome and α3β1 integrin in the actin filament-based focal adhesion. Both stable and transient interactions are required for directional persistence in keratinocyte migration and wound closure [65]. Inherited diseases such as junctional epidermolysis bullosa and laryngo-onycho-cutaneous syndrome which are associated with mutations in all chains of LM332 and mutations in the α3 chain, respectively, are characterized by excessive granulation tissue and chronic, slow-healing cutaneous erosions [69, 70]. Other minor laminins

play also important roles in wound healing. For example, it has been shown that reduced expression of LM111 and LM511 in corneal basement membranes of patients with diabetes is associated with delayed corneal epithelial wound closure [71]. The α5 laminin chain displays an increased ability to interact with cell surface receptors on endothelial cells and keratinocytes. LM511 co-operates with LM332 to support directional migration in epithelial cells [65, 72]. Laminins are also involved in blood vessel growth and maturation, a major process associated with wound healing. LM411 predominates in endothelial basement membranes with LM511 and LM3B11 being minor components in small vessels [65]. Although the α4 laminin chain has the lowest affinity for various cell surface receptors, it is critical for the proliferation, adhesion and migration of endothelial cells [65, 73, 74].

Matricellular proteins form a large class of modular proteins that can be found in the ECM, the inner plasma membrane and endoplasmic reticulum and in the nucleus participating in numerous cell functions [2, 28]. Matricellular proteins are minor components of adult tissues they exhibit increased expression in developing tissues as well as during pathologic processes including cancer, diabetes, hypertension, and wound healing [2, 28]. They bind to several matrix components, cell surface receptors, growth factors, cytokines and proteases controlling cell-cell and cell-matrix interactions. They are upregulated in the wound bed and it is believed that they do not contribute to ECM integrity, but are rather involved in the transient regulation of cell signaling, adhesion, migration and matrix biosynthesis. Matricellular proteins bind to and modulate signaling of soluble growth factors such as VEGF, FGF, and latent TGF-β . Notably, matricellular proteins can trigger growth factor receptor signaling both directly and indirectly [28]. For example, tenascin-X activates latent TGF-β via binding to cell surface α11β1 integrin and in turn promotes epithelial-to-mesenchymal transition (EMT) in mammary epithelial cells [75]. Thrombospondin 1 (TSP1) also activates latent TGF-β in cell-independent manner [76]. Matricellular proteins such as osteopontin, CCN2, TSP-1, and SPARC are also involved in development of fibrosis in patients suffering from metabolic diseases such as diabetes and obesity [77-83]. Osteopontin is involved in dermal fibrosis since it facilitates TGF-β-induced myofibroblast differentiation [84, 85]. It also augments fibroblast proliferation and migration and abrogation of its expression results in faster wound healing with less granulation tissue and scar formation [86, 87]. The matricellular protein CCN2 is also upregulated in the wound bed and its expression is associated with hypertrophic scarring and fibrosis [88, 89]. It stimulates the recruitment of differentiation of mesenchymal stem cells to fibroblasts in the wound bed. CCN2 also promotes fibroblast adhesion to fibronectin, as well as the expression of ECM molecules including collagen I, III, FGF and tissue inhibitors of MMPs (TIMPs) [90, 91]. In a recent study it has been shown that CCN2 induces cellular senescence in

fibroblasts that in turn adopt an anti-fibrotic "senescence-associated secretory phenotype" associated with upregulation of MMPs and downregulation of collagen, suggesting an anti-fibrotic role for CCN2 in a context-dependent manner [92]. Furthermore, CCN2 is also involved in re-epithelialization by promoting keratinocyte migration via interaction with α5β1 integrins [93]. SPARC is another matricellular protein upregulated in wounds and it is associated with the development of fibrosis. It promotes the biosynthesis of ECM molecules and collagen fibrillogenesis in dermal fibroblasts [94-96]. Another matricellular protein associated with fibrosis is periostin, which is accumulated in fibrotic dermis. Periostin supports Rho-associated protein kinase-dependent proliferation and myofibroblast persistence of hypertrophic scar fibroblasts, but not of normal dermal fibroblasts [97]. Tenascin-C is accumulated in wound edges promoting the migration of fibroblasts along fibrin-fibronectin rich matrices in early wounds. In contrast, degradation of tenascin-C in later stages of wound healing liberates fragments that inhibit the migration of fibroblasts [98, 99]. This dual role of tenascin-C seems to buffer fibroblast functions. The association of tenascin-C accumulation with fibrotic disease may be a result of persistent expression of tenascin-C, or a failure of its degradation by matrix proteases [100, 101].

Proteoglycans and hyaluronan

PGs are complex macromolecules consisting of a core protein to which one or more GAG chains are covalently attached. GAGs are long heteropolysaccharides that contain repeating disaccharide units composed of hexuronic acids (D-glucuronic acid or L-iduronic acid) and hexosamines (*N*-acetyl-D-galactosamine or *N*-acetyl-D-glucosamine) [100,101]. These polymers can carry sulfate groups in various positions of uronic acids and hexosamines provid them with high structural heterogeneity and high negative charge. There are six types of GAGs named chondroitin sulfate (CS), dermatan sulfate (DS), HS and heparin, the non-hexuronic acid-containing keratan sulfate (KS) and HA which is the only GAG present in free form not covalently bound onto a PG core protein [102, 103]. PGs are extremely heterogeneous in nature since they can carry more than one types of GAG chains and these chains can vary in length and fine structure. PGs are capable of interacting with a plethora of ECM molecules, cell surface receptors, growth factors and cytokines, either via their GAG chains or through their core protein thus regulating ECM organization, cell signaling, proliferation, adhesion, migration, survival and differentiation [102, 103]. According to their localization, PGs are divided to three categories: extracellular, cell surface and intracellular ones. Each PG category is then classified in subfamilies according to their protein sequence homology and the presence of unique protein modules [5, 103]. PGs

are important molecules that regulate cell-matrix interactions and are actively implicated in the wound healing process [5, 103].

Versican belongs to a subfamily of matrix secreted PGs named hyalectans. It can interact with HA and other matrix components and cell surface receptors creating large complexes that retain large amounts of water creating a viscous ECM. It is a versatile molecule that regulates cell signaling and motility [18, 103, 104]. Versican accumulates in hypertrophic burn scars and is produced in high amounts by deep dermal fibroblasts that are involved in the development of hypertrophic scars [105, 106]. Suppression of versican leads to a less aggressive growth of dermal papilla fibroblasts [107]. Furthermore, elevated levels of versican are associated with enhanced fibroblast migration and wound healing [108].

Another subfamily of matrix PGs are SLRPs. Decorin, biglycan and lumican are members of this subfamily and it has been shown to be involved in wound healing. Decorin, biglycan and fibromodulin are accumulated in the wound bed and their levels are modified during wound healing [109]. Biglycan is highly expressed in hypertrophic burn scars, whereas the levels of decorin and fibromodulin were significantly lower in hypertrophic scars compared to normal skin [105, 110]. Decorin is expressed late during wound healing in burn scars [111]. *In vivo* experiments in decorin knockout mice demonstrated that decorin is important for cutaneous wound healing and its loss is associated with delayed wound healing [112], whereas decorin deficient fibroblasts demonstrate increased adhesion to collagen and fibronectin and enhanced rates of proliferation and migration [113]. It has been also shown in tendon injury that biglycan and decorin are critical for proper healing at younger ages. In aged mice, the presence of both molecules is beneficial only in early-stage healing and is inadequate to promote late-stage healing [114]. Decorin binds TGF-β acting as a natural inhibitor for this growth factor, thus buffering its function during wound healing and preventing fibrosis. Decorin transfection decreased the TGF-β-induced expression levels of profibrogenic genes such as fibronectin, collagen type I, III, and IV in corneal fibroblasts as well as their differentiation to myofibroblasts. Furthermore, SLRPs as decorin, lumican and fibromodulin play a critical role in collagen fibrillogenesis and proper architecture of collagen fibers [5, 103]. Their levels may be essential for proper organization of collagen fibers during normal wound healing whereas disturbance of their amounts may result in a less organized and fibrotic ECM observed in keloid tissue and hypertrophic burn scars [105, 115]. Lumican promotes fibroblast activation and contraction in an integrin α2-dependent mechanism [116]. Lumican-deficient mice exhibit delayed corneal and skin wound healing, abnormal collagen fibrils and fragile skin [117, 118]. The absence of lumican leads to decreased apoptosis of fibroblasts and keratocytes, reduced recruitment of macrophages and neutrophils and modulation of Fas-FasL signaling suggesting a role for lumican in

fibrotic healing [117]. In addition, SLRPs can bind directly to various growth factors receptors such as EGFR, VEGFR2, IGF-IR and innate immune system receptors like TLRs modulating cell signaling, evoking autophagy and promoting the secretion of pro-inflammatory mediators involved in wound healing [119, 120]. All these functions may differentially regulate excessive angiogenesis, cell proliferation and ECM production in the wound bed.

Cell surface PGs are categorized mainly into two major subfamilies named syndecans and glypicans. Syndecans consist of four members and they are transmembrane PGs carrying mainly HS chains [119]. Through their HS chains, they can bind numerous ECM components, soluble ligands including interleukins, FGF, VEGF, TGF-β, Hedgehog and Wnt and may interact laterally with other receptors such as FGFR, EGFR, integrins and stretch-activated calcium channels of the TRPC family. So, syndecans can act as co-receptors for growth factors and ECM molecules promoting signaling and regulating a plethora of cell functions [6, 121, 122]. Syndecans are upregulated during tissue injury and play crucial roles in wound healing. Syndecan-1 and -4 are upregulated in skin wounds and are involved in re-epithelialization [123]. Syndecan-1 deficiency is associated with compromised adhesion, migration and differentiation of keratinocytes and delayed re-epithelialization [124, 125]. On the other hand, over-expression of syndecan-1 delays epidermal wound healing due to increased proteolytic shedding of syndecan-1 ectodomain that in turn inhibits cell proliferation [126]. Similarly, knockout of syndecan-4 leads to delayed skin repair affecting fibroblasts migration, granulation tissue and angiogenesis, but also reduces the ability to exert tension on the ECM [127, 128]. Syndecans also regulate growth factor activities to promote wound healing. For example, when syndecan-4 is activated by FGF-2 augments wound healing by activating dermal fibroblasts adhesion and producing ECM [127]. Syndecan-4 binds tenascin-C and fibronectin, promoting wound healing in fibroblasts [129]. Both syndecan-2 and -4 co-operate with integrin $\alpha5\beta1$ to bind a transglutaminase-fibronectin rich matrix and to induce cell adhesion and fibronectin deposition during epidermal wound healing [130]. Syndecan-1, via interaction with $\alpha v\beta3$ and $\alpha v\beta5$, promotes smooth muscle and endothelial cell activation and vasculature regeneration [131, 132]. Syndecan-1 and -4 knockout mice show functionally adverse infarct healing in the heart and syndecan deficiency is associated with less organized collagen fibers susceptible to MMP degradation, hampered granulation, attenuated myofibroblasts differentiation and contractility, that ultimately lead to cardiac dilatation and rupture [133, 134]. Both syndecan-1 and -4 are involved in the activation of pro-fibrotic signaling to cardiac fibroblasts inducing ECM production, matrix contraction, differentiation to myofibroblasts and heart fibrosis [16]. Activation of the renin-angiotensin-aldosterone system and production of angiotensin II is a potent pro-fibrotic signal that requires the presence of

syndecan-1 to stimulate cardiac fibrosis by enhancing TGF-β signaling, biosynthesis of collagens and secretion of CCN2 [135]. On the other hand, the pro-fibrotic role of syndecan-4 is mediated by binding to calcineurin via its cytoplasmic domain and activation of calcineurin-nuclear factor of the activated T-cells (NFAT) signaling pathway to promote myofibroblast differentiation, collagen production and myocardial stiffness [136]. Syndecan-4 can also regulate the pro-fibrotic events in fibroblasts through inhibition of calcium influx via the transient receptor potential canonical (TRPC) 7 cell membrane channel. Syndecan-4 induces protein kinase Cα (PKCα) to phosphorylate TRPC7, thus controlling cytosolic calcium levels and myofibroblasts differentiation as well as keratinocytes adhesion and differentiation [137]. In contrast to its full-length form, syndecan-4 fragments shed from the cell surface upon the action of matrix-degrading enzymes inhibit the proliferation of cardiac fibroblasts, reduce the expression of collagen I and III and upregulate the ratio of MMPs to TIMPs to favor matrix degradation [138].

Serglycin represents the only characterized intracellular PG so far. Serglycin is localized into secretory granules of inflammatory cells and platelets, is secreted by dermal fibroblasts upon UVB exposure and is involved in tissue repair [139]. It is co-localized into α-granules of platelets with bioactive molecules including fibronectin, PDGF, CXCL7, CXCL4, RANTES/CCL5 and CCL3 and is essential for their storage and effective platelet aggregation and leukocyte activation [139, 140]. Apart from binding to inflammatory mediators and directing their bioavailability and functions within ECM, serglycin is also capable of directly interacting with ECM molecules. It binds to collagen I and collagen-like structures of other proteins affecting cell functions and immune system response [141, 142]. This implies that serglycin is strongly implicated in the inflammatory phase of wound healing process, as well as in the tissue remodeling phase, since it mediates endothelial cells' functions [143, 144].

HA is is synthesized by three HA synthases (HAS1-3) at the cytosolic part of the cell membrane in mammals [145]. HA has a dual role and is involved in both fibrotic and regenerative wound healing. For example, oral fibroblasts that promote rapid and scarless wound healing don't express HAS and have decreased pericellular HA amounts [146]. In contrast, fetal scarless wound healing is associated with increased amounts of HA, and in vitro treatment of adult wounds with amniotic fluid enriched in HA markedly improved re-epithelialization [147, 148]. It has been shown that HA of different size has opposite effects in various cellular functions and wound healing. Large molecular-weight HA is correlated with decreased inflammation, increased expression of collagen III and TGF-β3 activity that has anti-fibrotic action, whereas low molecular weight HA exhibits increased inflammation, collagen I synthesis, increased proliferation of fibroblasts and differentiation to myofibroblasts, promoting a

fibrotic cell phenotype [149, 150]. Actually, at sites of inflammation low molecular weight HA binds to TLR2/4 and activates signaling cascades that promote the release of the pro-inflammatory cytokines interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and IL-1β, that in turn stimulate HA production in various cell types [27, 151]. Accumulation of HA is observed in fibrosis and the failure to remove HA fragments by CD44 and TLRs contributes to persistence of inflammation and destruction observed in tissue fibrosis [152, 153]. Although HA binds to CD44 and RHAMM and signals through them, HA also seems to be essential for TGF-β-induced fibroblast differentiation into myofibroblasts [154-156]. It is suggested that HA regulates TGF-β signaling by inducing a co-localization and interaction of the receptors CD44 and EGFR within lipid rafts [157, 158]. HAS2 is also involved in the development of lung fibrosis. Deletion of HAS2 abrogated the invasive fibroblast phenotype, impeded myofibroblast accumulation, and inhibited the development of lung fibrosis in a CD44-dependent manner [159]. In another study, it has been shown that HAS2 is important for TGF-β-induced mesenchymal differentiation and migration of NMuMG mammary epithelial cells in a CD44- and HA-independent manner [160].

Matrix Proteases

Several proteolytic enzymes are involved in wound healing. MMPs belong to the metzincin family of metalloproteinase that present a zinc-binding motif at their active site. Plasminogen activators such as urokinase-type plasminogen activator (uPA) and tissue-type urokinase activator (tPA) are serine proteases. They are involved in the activation of plasminogen to plasmin and cleavage of fibrin polymers as well as degradation of various ECM components and activation of MMPs [2, 9]. MMPs are central players of healing process in the wound bed and are differentially expressed by all cell types in a time- and context-dependent manner. Apart from regulating ECM turnover, they control inflammation, cell migration and angiogenesis by acting on growth factors, cytokines, and cell surface receptors [161]. MMPs activity on various ECM components liberates active fragments called matrikines that regulate various cell functions during wound healing [12]. MMPs are involved in all phases of wound healing and their abnormal expression and functions are involved in dysfunctional wound repair and the development of chronic wounds or fibrosis, hypertrophic scars and keloids in skin. Scarless fetal wounds have a greater expression ratio of MMPs to TIMPs, which favors cell migration and ECM turnover compared to scarring wounds [162]. Chronic ulcers also exhibit increased activity of MMPs and other proteases [163]. It has been shown in a type 2 diabetic rat model that elevated MMPs expression is associated with delayed wound healing and development of diabetic chronic wounds [164].

Hypertrophic scars are also characterized by constant MMPs activity [161]. For example, elevated MMP-9, and MMP-13 gene expression is observed in fibroblasts isolated from the margins of the original keloid wound and their expression is markedly downregulated upon treatment with decorin [165]. MMP-9 is recruited to the surface of fibroblasts and activates TGF-β signaling that in co-operation with other ECM signals promotes fibroblasts contraction, fibronectin expression and myofibroblast differentiation [166, 167]. On the other hand, the levels of MMP-1 are decreased in hypertrophic scar tissue and stimulation of MMP-1 expression reduces fibrosis and hypertrophic scars [168-171]. Wound closure is severely affected in mice deficient in MMP-8, and it is associated with a delay of neutrophil infiltration during the first days and a persistent inflammation at later time points [172]. MMP-8 acts as an anti-fibrotic protease due to the degradation of pro-inflammatory cytokines. Likewise, MMP-9 null mice display delayed wound healing associated with compromised re-epithelialization, reduced clearance of fibrin clots and abnormal matrix deposition [173]. MMPs are important for re-epithelialization of various tissues in a tissue-dependent manner. For example, MMP-1 and MMP-7 are important for re-epithelialization in skin and mucosal epithelia, respectively, via different mechanisms involving integrin $\alpha 2\beta 1$ [161]. Keratinocytes bind to collagen I in the dermis via integrin $\alpha 2\beta 1$ upon basement membrane disruption in the wound bed. MMP-1 is induced in keratinocytes at the wound edge and cleaves collagen I. As a consequence, the collagen triple helix partially unwinds and reduces the avidity of integrin $\alpha 2\beta 1$ ligation. This drives keratinocytes to interact via integrin $\alpha 2\beta 1$ with intact collagen I within the open wound bed thus promoting keratinocyte migration [161, 174-176]. MMP-7 expression is critical for re-epithelialization in mucosal epithelia. MMP-7 sheds syndecan-1 from epithelial cells, and this process attenuates the activation of integrin $\alpha 2\beta 1$, thus decreasing its interaction with ECM components and facilitating cell migration [161, 177, 178].

Epigenetic reprogramming during wound healing

In recent years, a large number of publications has focused on the area of epigenetic therapy, which is not surprising since it links alterations in chromatin structure to the cell phenotype and numerous functions of a given biological system [179, 180]. It is of fundamental and of great clinical relevance to perceive how these changes are orchestrated. Epigenetic regulation is an important driver of the wound healing response; however, many mechanistic details remain to be elucidated. Common and highly interdependent epigenetic mechanisms that are closely associated with gene expression include DNA methylation, post-transcriptional histone modifications and regulatory non-coding RNAs (ncRNAs) [181-185]. The dynamic interplay among these epigenetic mechanisms regulates chromatin remodeling and

consequently can alter the expression status of large numbers of transcription factors and signal transduction molecules [182, 186, 187]. In this review, we focus our attention on the most extensively characterized subfamily of ncRNAs, named microRNAs, since they have been thoroughly studied among epigenome components in the context of wound healing and regenerative medicine [188]. They are endogenous small ncRNAs molecules, 17-25 nucleotides long, which have an important role in post-transcriptional regulation of a wide range of cellular processes [189]. Interestingly, more than 60% of protein-coding mRNAs may be targets of miRNAs as indicated by bioinformatics predictions, thus participating in various signal transduction pathways both in physiological and pathological conditions [190, 191]. The miRNA processing pathway has long been viewed as linear and universal to all mammalian miRNAs. As illustrated in Figure 2, this canonical maturation cascade includes the production of the 70-nucleotide primary miRNA (pri-miRNA) transcript, its cleavage to the precursor hairpin (pre-miRNA), transfer to the cytoplasm and finally the cleavage of the pre-miRNA to its mature length. The functional strand of the mature miRNA is loaded together with Argonaute proteins into the RNA-induced silencing complex (RISC), where it guides RISC to target mRNAs [192-195]. Depending on the complementarity, miRNAs can induce mRNA degradation via the RNA-induced silencing complex, translational repression, or total inhibition of mRNA translation [196, 197].

Epigenetic regulators appear to be involved in the wound healing and skin repair processes, thus dynamically regulating dermal regeneration. More specifically, wound healing and fibrosis are evidently regulated by a wide range of miRNAs, either in a direct or indirect way (Table 1). Individual miRNAs have been associated with distinct phases of wound healing, including inflammation, cell proliferation and tissue regeneration, serving themselves as target biomarkers for systematic regulation of wound repair and fibrosis [186]. For instance, miR-21 is the principal regulator of fibroblast migration and it inhibits the epithelialization in skin wound [198]. Moreover, it mediates fibroblast activation in pulmonary fibrosis, therefore it is characterized as a pro-fibrotic factor [199]. Self-limited and rigorously regulated inflammation is an initial step for proper wound repair, since chronic inflammatory responses may lead to overacting wound healing and loss of the regeneration process. Emerging evidence has shown that miRNAs may regulate inflammation through distinct mechanisms. For example, miR-146a abolishes the activation of the nuclear factor κB (NF-κB) pathway, which is the central signal transduction pathway of inflammation [200, 201]. Moreover, miR-146a induces the expression of the pro-inflammatory cytokine IL-10 and modulates the IL-1β signaling pathway [202, 203]. Recent reports indicate that miR-142-5p and miR-130a-3p may act as pro-fibrotic modulators by regulating macrophage functions via IL-4 and IL-3 expression [204]. Another interesting example is miR-29, which is linked to the pathogenesis of fibrosis

by regulating ECM production and deposition and EMT. Its decreased expression in cardiac, renal, pulmonary and liver fibrosis, is followed by the upregulation of collagen type I and IV expression levels, affecting the severity of fibrosis in numerous organs [205-208]. Serum miR-29 levels are much lower in patients with advanced liver fibrosis compared to healthy controls [209]. Notably, the estradiol-stimulated miR-29 overexpression in liver cells of a mouse model may answer the question whether women are more susceptible to alcohol-induced liver fibrosis than men [210]. These findings suggest that miR-29 may act as an anti-fibrotic epigenetic modulator (Table 1), serving as a prognostic and potential therapeutic biomarker. Moreover, critical for the recovery of cells during wound healing is the cell proliferative phase, since it is necessary to rapidly restore an organ function. It has been reported that miR-203 may act as a pro-proliferative and pro-migratory factor in cutaneous wound healing and miR-483-3p controls keratinocyte proliferation during the re-epithelialization of wound healing process [211, 212]. To summarize, evidence suggests that miRNAs participate and regulate all phases of wound healing. Therefore, understanding the molecular context of their functions could be advantageous for tissue regeneration applications.

Extracellular matrix regulation by miRNAs

Considering the mechanism of miRNA function, which is based on the post-transcriptional regulation of RNA expression and translation (Figure 2), it is not surprising that they have been implicated in the regulation of ECM protein and glycan expression. Different modes of regulation have been described, including a direct targeting of ECM mRNAs, indirect regulation of ECM constituents via miRNA-dependent targeting of transcriptional activators and repressors, epigenetic regulation of ECM-targeting miRNAs, and co-regulation of miRNAs with ECM receptors (Figure 3) [247]. In addition, the pattern of miRNA expression within a given tissue and cell type can be regulated by via the 3' UTR of selected ECM mRNAs, such as versican and CD44, and by matrix-mediated signaling processes [247-249]. In this section, these modes of regulation using selected examples of miRNA-dependent ECM molecules with relevance for wound repair are presented and critically discussed.

Among the miRNAs directly regulating gene expression via induction of mRNA degradation through their 3'UTR (Figure 2), the miR-29 family represents an important member targeting multiple ECM molecules. miR-29c downregulates two fibrillary collagens with particular importance for wound repair [216], collagen type I and type III [250-253], resulting in effects on cell motility and a modulation of cardiac fibrosis in different experimental models. miR-29 also plays a role in the regulation of proteolytic factors which are relevant during the phase of collagen remodeling and angiogenesis of skin wound repair. Both

'sheddases' capable of releasing the extracellular domain of syndecans [126, 254] and MMPs processing fibrillary collagens, such as collagen I and collagen III, are of importance in this context. miR-29 is capable of directly targeting MMP-2 mRNA [122], whereas an indirect mode of MMP regulation by this miRNA has been described for aortic smooth muscle cells. Treatment of these cells with oxidized LDL resulted in miR-29b-mediated downregulation of DNA methyltransferase 3b [231]. The resulting epigenetic changes at lead to a differential regulation of MMP-2 and MMP-9. Finally, miR-29a/b/c co-regulates laminin LAMC2 and integrin α6 in head and neck squamous cell carcinoma [255], representing an example for a regulation of an ECM compound and its receptor by a miRNA [65, 256].

An additional multifunctional miRNA with relevance for ECM function is miR-10b. miR-10b mediates downregulation of the transcription factor HOXD10, resulting in an indirect upregulation of MMP-14 and uPA activator receptor (uPAR) in breast cancer and glioma cells [257, 258], thus influencing the proteolytic milieu. In addition, upregulation of miR-10b in breast cancer and endometriotic cells resulted in a direct targeting and downregulation of syndecan-1 as demonstrated by 3' UTR luciferase reporter assays, qPCR, flow cytometry and immunofluorescence microscopy [259, 260]. In both cases, cell motility and invasive growth of the syndecan-1 depleted cells were affected, which could be attributed to a multitude of effects, including altered signaling via receptor tyrosine kinase, focal adhesion kinase/Rho and IL-6 signaling pathways as well as alterations in the proteolytic milieu that were due to reduced expression of this multifunctional co-receptor. miR-10b-dependent targeting of syndecan-1 may be relevant to wound repair, as it regulates angiogenesis, wound re-epithelialization and recruitment of inflammatory cells during skin wound healing and cardiac repair [124, 126, 134]. Syndecans are also regulated by miR-143 and miR-145. Indeed, these miRNAs are thought to be functionally linked and co-regulated in a bicistronic manner [261]. miR-143 and miR-145 target syndecan-1, resulting in a reduction of cell growth in melanoma, urothelial carcinoma and ovarian cancer, respectively [262-264]. TGF-β-inducible miR-143 was also shown to target additional syndecan family members, including syndecan-4, involved in modulating fibroblast function during skin wound repair [127], and versican in a zebrafish model, where it had an impact on the glomerular filtration barrier [265]. Moreover, miR-143 and miR-145 have an impact on the proteolytic milieu, as evidenced by the regulation of MMP-13 [224] and the inhibitor PAI-1 [231], respectively. Syndecan-1 is a good example of a matrix receptor that can influence the expression of miRNAs and their respective targets. It acts upstream of some microRNAs, resulting in their altered expression. This was demonstrated in the case of prostate cancer cells, in which syndecan-1 silencing induced downregulation of the miRNA processing enzyme Dicer. The associated change in the levels of mature miR-331-3p and its targets

resulted in the induction of EMT [266]. Moreover, aberrant syndecan-1 expression has been linked to the expression of miR-126 and in prostate cancer, with an impact on cell proliferation [267]. Finally, syndecan-1 has been identified as part of a regulatory loop comprised of MMP-9 and miR-494, which regulated irradiation-induced angiogenesis in medulloblastoma [268]. As recent reports indicate that syndecan-1 and the syndecan-processing enzyme, HPSE, are mechanistically involved in the biogenesis of exosomes [269, 270], it is tempting to speculate that this PG may also effect secretion of a multitude of miRNAs via this process.

Collagens of the dermis play important roles by providing structural support for resident cells and for inflammatory and accessory cells during the remodeling phase of wound repair [271, 272]. Among the various collagen types found in vertebrates, the fibrillary collagens type I and type III play prominent roles during wound repair [272]. For example, direct regulation of collagen type I expression via binding of the miRNA seed sequence to the 3' UTR of mRNAs encoding one of the three chains of these triple-helical structural proteins was demonstrated for let-7g (COL1A2), miR-29c (COL1A1, COL1A2) and miR-133a (COL1A1) [250-253], resulting in effects on cell motility and a modulation of cardiac fibrosis in different experimental models. Blood-derived fibrin and fibronectin form a provisional ECM in the initial stage of skin wound healing [272]. While a quantitative regulatory effect of miRNAs on these molecules at this stage appears unlikely considering the large quantities of blood-derived matrix proteins, miRNA-mediated modulation of fibronectin expression may be of importance at later stages of repair, affecting the migratory behavior of cells in the granulation tissue and wound edges. Indeed, several miRNAs have been shown to directly target fibronectin, resulting in altered cell survival and migration, including miR-17 in a transgenic mouse model [273], miR-146a in diabetic animals [274], and miR-206 in bronchopulmonary dysplasia [275]. In several cases, the mesenchymal marker fibronectin is indirectly regulated via microRNAs affecting the process of EMT, as exemplified by the case of miR-200b in renal fibrosis [276] and miR-7 in breast cancer [277].

As a final example for regulatory modes exerted by ECM compounds and their receptors, the concept of competing endogenous RNAs, or ceRNAs is also discussed here. As a prime example, the 3' UTR of versican mRNA acts as an endogenous microRNA sponge, thus sequestering miRNAs and neutralizing their activity. This has been shown by over-expression of versican 3' UTR in diverse systems, resulting in a neutralization and target suppression of the microRNAs miR-199a [278] (regulating versican and fibronectin), miR-133a, miR-144 and miR-431 [279]. Of particular relevance for wound repair were experiments by Yang and Yee [108], who demonstrated enhanced wound closure and fibroblast migration in cells and transgenic mice expressing versican 3' UTR. This phenotype was apparently due to

binding of numerous miRNAs to the ceRNA, including miR-185, miR-203, miR-690, miR-680 and miR-434-3p, resulting in an upregulation of versican itself and of the Wnt signaling effector beta-catenin. Another example for a ceRNA is CD44. Interactions between this transmembrane receptor and its ligand HA regulate several aspects of wound repair, including chemotaxis and cell migration, collagen secretion, inflammation and angiogenesis [271]. CD44 mRNA acts as a ceRNA capable of neutralizing miRNAs, as has been shown miR-216a, miR-328, miR-330, miR-491, miR-512-3p, miR-608 and miR-671. As a consequence, the 3' UTR of CD44 upregulated not only the expression of CD44 itself, but also of fibronectin and COL1A1, with possible relevance for wound repair [280, 281]. Moreover, CD44 is also directly targeted by several miRNAs including miR-34, miR-199a-3p, miR-328, miR-373 and miR-520c [282-285], resulting in effects on cell migration, proliferation and stem cell phenotype. Since it is a carbohydrate, expression of HA is not directly modulated by miRNAs, but via regulation of their biosynthetic enzymes, the HASes [286]. In breast and cervical cancer cells, inhibition of the miRNA let-7 resulted in a suppression of its target HAS2, with an impact on cell survival, adhesion and invasive behavior [287]. Moreover, the targeting of HAS2 by miR-26b resulted in increased ovarian granulosa cell apoptosis [288], whereas targeting of HAS2 by miR-23a-3p caused cellular senescence, with possible implication for skin aging and repair [289]. Finally, the interaction of HA with CD44v3 in head and neck squamous cell carcinoma has been shown to have an indirect regulatory impact on the expression of miR-302 via pluripotency-associated transcription factor induction [290], providing another example for matrix-dependent signaling processes that regulate miRNA expression patterns.

MicroRNA - ECM interactions in wound healing

As mentioned above, wound repair is characterized by several successive phases, during which individual matrix molecules and miRNAs play distinct roles [291, 292] (Table 1, Figure 1). The earliest stage is characterized by hemostasis and inflammation. While it is unlikely that miRNAs play a role in regulating the amount of these largely blood-derived ECM molecules during the hemostasis stage, it can be envisaged that the presence of these matrix constituents can influence the miRNA expression pattern in cells recruited to the wound (Figure 3). For example, the presence of thrombospondin-1 affects the miRNA expression profile of vascular smooth muscle cells [293]. Platelet activation and degranulation subsequently trigger the recruitment of different classes of leukocytes as part of an early inflammatory response. A recent study on *Staphylococcus aureus* clearance at skin wound sites has revealed a role for miR-142-3p in neutrophil recruitment [294]. Using miR-142-3p-deficient mice, the authors could demonstrate that targeting of cytoskeletal elements and Rho-GTPase signaling

compounds affected leukocyte recruitment. While not explored in this study, a targeting of integrin αv by this miRNA may impede recruitment of epithelial cells during wound repair by hindering cellular interactions with the ECM, including vitronectin, fibronectin and thrombospondin in the provisional wound matrix [295]. Likewise, altered expression of miR-223, which is upregulated in the inflammatory phase in human skin [296] could potentially affect β1 integrin expression and cell motility [297, 298], as well as myeloid-derived suppressor cell differentiation [299]. Another microRNA which is upregulated during early skin wound repair both in mouse models and humans is miR-155 [300, 301]. Apparently, an inhibition of miR-155 has beneficial effects on wound repair, as application of a miR-155-inhibitor reduced inflammatory cell recruitment into the wound and improved the structural quality of the regenerated tissue [302]. Likewise, miR-155-deficient mice showed more rapid and qualitatively improved wound repair, as evidenced by increased collagen I deposition [301]. In contrast, another study employing a miR-155 expression plasmid during cutaneous wound repair reported an acceleration of keratinocyte migration, which was attributed to an inverse regulation of MMP-2 and TIMP-1 [303]. The context-dependent effects may be due to the mode of experimental miR-155 modulation. In addition, additional targets of miR-155 may have contributed to the phenotype. Importantly, HPSE was shown to be regulated by a miR-155-based artificial miRNA, resulting in an inhibition of melanoma cell adhesion, migration and invasiveness [304]. Moreover, miR-155 regulates additional MMPs, which may have differentially affected wound repair in the partially conflicting studies [305].

At the late inflammatory stage of wound repair, inflammation needs to resolve, and several miRNAs contribute to this process (Figure 1). Notably, miR-21 is upregulated by macrophages upon phagocytosis of apoptotic neutrophils and contributes to the resolution of inflammation via the upregulation of anti-inflammatory cytokines such as IL-10 [306]. Expression of miR-21 is modulated by decorin during inflammation [307] and it has been shown to target the HS editing enzyme HSulf1, with a possible impact on HS-dependent signaling processes during wound repair [308]. Indeed, as pointed out before, both syndecans and decorin play a prominent role in wound repair and transgenic and knockout mouse models that display a wound healing phenotype [112, 124, 126, 127, 134]. Another miRNA involved in the resolution of inflammation during wound repair is miR-132, which is upregulated in several leukocyte subsets during the inflammatory phase of wound repair. While it primarily attenuates inflammation by promoting M2 polarization of macrophages and by preventing the overshooting production of pro-inflammatory cytokines [309, 310], the targeting of MMPs, such as MMP-9 and MT3-MMP/MMP-16 that was demonstrated in different experimental systems [311, 312], may additionally contribute to the resolution of inflammation in the context of wound repair. Since expression of miR-99

family members has been linked to the activity of several integrin subtypes, including β4 and αvβ3 integrin [313, 314], it may be worth evaluating whether downregulation of miR-99a, miR-99b and miR-100 during the inflammatory phase is linked to altered integrin-ECM interactions [315]. Moreover, miR-146a, which is also downregulated during this phase of skin wound repair [316], may contribute to the resolution of inflammation as a negative regulator of several compounds of the proinflammatory NF-κB-pathway in keratinocytes and macrophages [317, 318]. miR-146a has also been described as a regulator of the PG aggrecan [319], reported to contribute to a block of dermal repair in ADAMTS-5-deficient mice via an effect of fibroblast differentiation from progenitor [320]. However, the relevance of this finding in the context of the inflammatory phase of wound repair is unclear.

The shift in the cytokine profile linked to the differentiation of macrophages to a more reparative phenotype affects the proliferation of fibroblasts in the granulation tissue, the ECM production by these cells, and the induction of angiogenesis [291, 292]. Several miRNAs are upregulated during the phase of proliferation and re-epithelialization in skin wound repair (Figure 1). For example, miR-21 is upregulated in keratinocytes and mesenchymal cells of the wound edge, where it promotes cell migration [321, 322]. While it remains to be shown whether decorin, which has been linked to this miRNA [247] play a role in this process, it has been demonstrated that miR-21 inhibition does not only delay re-epithelialization and hinders contraction of the wound, but also affects collagen deposition, thus promoting cell adhesion and migration [321]. Another miRNA that is upregulated in proliferating keratinocytes is miR-31. While its mechanism of action involves a targeting of epithelial membrane protein-1 [323], it is noteworthy that miR-31 has been shown to target several integrin α subunits (α2-, α5, αv-) and β1-integrin in diverse experimental systems [324]. This suggests that integrin dysregulation may have additionally contributed to altered matrix-dependent cell spreading, collagen adhesion and proliferation. Likewise, downregulation of miR-99 family members may not only stimulate keratinocyte proliferation via upregulation of the miR-99-repressed signaling compounds Akt and mTOR [315], but also of several integrins [313, 314].

Angiogenesis is a pivotal aspect of the proliferative phase of wound repair, as it ensures a supply of nutrients for proliferating keratinocytes, fibroblasts and immune cells. ECM compounds such as pro-angiogenic integrins, MMPs and PGs such as versican, decorin and syndecans are important modulators of angiogenesis [112, 126, 325]. During skin wound repair, miR-199a-5p is downregulated in the dermis and endothelium, and it was shown that this miRNA inhibits angiogenesis via negative regulation of the transcription factor ETS1 [326], which is a known inducer of ECM proteins in fibroblasts, including collagen I α2, TGF-β induced protein, lumican and decorin [327]. Moreover, miR-199a-5p

downregulation exerts a proangiogenic effect during wound repair via upregulation of MMP-1 [326]. Like miR-199-5p, miR-200b targets ETS1 in addition to VEGFR2 [328]. As miR-200b also regulates decorin [329] and fibronectin [276, 330] in other experimental systems, dysregulation of these ECM compounds may additionally contribute to the angiogenic process and wound re-epithelialization.

Probably the most profound changes in miRNA-regulated ECM deposition are observed in the final remodeling phase of wound repair, during which collagen III is replaced by the structurally more stable collagen I under the influence of growth factors, such as TGF-β, which promote ECM synthesis [272, 291]. A prominent miRNA involved in this process is miR-29b, which targets Col3α1, Col4α1, Col4α2 and Col5α1 [191, 331-333]. The relevance of miR-29b for wound repair become also apparent in a rodent wound model, were therapeutic application of this miRNA in a collagen scaffold increased the ration of collagens III and I. This was associated with a reduction of wound contraction and an overall improvement of remodeling [333]. Notably, miR-29b is known to target TGF-β, the integrin subunits α6 and β1 and the MMPs MMP-2 and MMP-9, which may have additionally contributed to altered remodeling [255, 332, 334, 335]. An indirect impact of a miRNA on remodeling has been uncovered for miR-1908, which targets the protein SKI, a regulator of collagen synthesis [336]. miR-1908 increased scar-derived fibroblast proliferation and production of TGF-β and collagen I [337] and reduced scar formation in a rat model of wound repair [336]. In addition, application of miR-1908 inhibitors to burn-wound scars in rats reduced their size and fibrosis [337], suggesting that miR-1908 as a promising potential therapeutic target and tool in wound repair.

The dysregulation of miRNAs' expression and their ECM targets has been linked to wound healing complications, such as hypertrophic scarring, keloid formation, and chronic non-healing wounds [338]. The aforementioned miRNA miR-29b is one of 92 miRNAs which are differentially regulated between hyperplastic scars and normal skin [339]. *In vitro* data suggest an anti-fibrotic effect of this miRNA, as its upregulation in primary human endometrial stroma cells reduced expression of Col1α1 and αSMA, thus contributing to an apoptosis-induction and inhibition of myofibroblast-like cell proliferation [340]. Importantly, in a murine thermal injury model, it was downregulated in thermal injury tissue, whereas miR-29b treatment promoted wound repair and inhibited scar formation. At the molecular level, this improvement could be linked to inhibition of the TGF-β-SMAD-CTGF signaling pathway, resulting in a suppression of collagen deposition [341]. As discussed above, a targeting of integrins, LOX and MMPs may have additionally contributed to preventing overshooting repair and fibrosis in this context. The TGF-β-inducible miRNA, miR-145, is upregulated in hypertrophic scars compared to healthy skin [342]. miR-145 is known to influence the proteolytic milieu by downregulating PAI-1, ADAM-17 and the HSPG

syndecan-1 [263, 343-345], and has been shown to influence ECM biosynthesis in cartilage by targeting the master regulator SOX9 [346]. In the context of hypertrophic scarring, the inhibition of collagen biosynthesis by PPARγ agonists is apparently due to a targeting of the TGF-β signaling mediator SMAD3 by miR-145 [347]. Moreover, myofibroblasts subjected to miR-145 inhibition were characterized by a reduced expression of TGF-β1 and collagen I and decreased contractility and migration [342]. Another miRNA linked to altered TGF-β expression and hypertrophic scarring is miR-200b, an important modulator of EMT [348, 349]. miR-200b was shown to be downregulated in hypertrophic scar tissues and human hypertrophic scar fibroblasts and its downregulation in fibroblasts occurs in a TGF-β-dependent manner [330, 350]. Functional *in vitro* analysis revealed that this miRNA regulated apoptosis and proliferation of human hypertrophic scar fibroblasts by altering collagen I and III as well as fibronectin expression in a TGF-β-dependent manner [330]. Similarly, miR-143-3p expression is downregulated in hypertrophic scar tissues, and its upregulation in hypertrophic scar fibroblasts is associated with a reduction in collagen I, III and αSMA, due to CTGF targeting [351]. Another miRNA downregulated in hypertrophic scars is miR-185. Following bioinformatics target prediction analysis, miR-185 could indeed downregulate expression of TGF-β and collagen I in fibroblasts, affecting cell proliferation and apoptosis [352]. The proteolytic modulation of collagen function is regulated my miRNAs miR-10a and miR-181c, which affect this process in hypertrophic scar fibroblasts by targeting PAI-1 and uPA and increasing MMP-1 levels [353]. Hypertrophic scars exhibit a lower expression of the PG decorin compared to healthy tissue [354] and it has been shown that decorin reduces hypertrophic scarring by modulating TGF-β functions [355, 356]. Notably, miR-181b, a miRNA that is upregulated in hypertrophic scars, was shown to target decorin. The authors demonstrated that miR-181b inhibition in hypertrophic scar fibroblasts reversed not only TGF-β-mediated downregulation of decorin, but also myofibroblastic differentiation [357].

Keloids represent another form of excessive scarring, and miRNA-mediated dysregulation of ECM molecules has been shown to be involved in keloid formation [358]. Being defined as benign dermal scars capable of invading adjacent healthy tissue, their formation is due to aberrant production of ECM by fibroblasts [359]. Among the miRNAs involved in the regulation of collagen production are miR-7, miR-29a and miR-196a, which are downregulated in keloid fibroblasts and modulate collagen type I and III production [227]. Notably, inhibition of miR-7, which is also regulating fibronectin expression in other experimental systems [277], leads to increased collagen type I alpha 2 expression in dermal fibroblasts [360]. While the decorin-modulated miRNA miR-21 promotes keloid fibroblast proliferation [361, 362], miR-199-5p, a miRNA targeting MMPs and DDR1 [363], inhibit this process. Interestingly, the

upregulation of miR-21 in keloid keratinocytes resulted in the induction of an EMT-like process and an enhanced stem cell phenotype, which could be partially linked to an upregulation of the HA receptor CD44 [364]. Consequently, migration, invasion and sphere-forming abilities of keloid keratinocytes were enhanced, which suggests that aberrant expression of miR-21 may account for the invasion and recurrence of keloids. Overall, these data provide strong evidence for a role of dysregulated miRNA expression in overshooting collagen production in keloids.

Another form of aberrant wound healing is associated with diabetes, as diabetic patients frequently suffer from impaired wound repair [365]. Indeed, the miRNA expression pattern in wound tissue of diabetic rats subjected to cutaneous wounding differs from their normal counterparts [366]. Among the differentially regulated miRNAs, miR-26a was shown to target the TGF-β signaling pathway compound SMAD1 [367], with an impact on the cell cycle and a potential impact on ECM biosynthesis. Consequently, miR-26a inhibition resulted in improved wound repair, including increased granulation tissue formation and angiogenesis. Interestingly, miR-26a also contributes to the progression of diabetic nephropathy in humans and mouse models through enhanced TGF-β/CTGF signaling, which results in altered collagen synthesis [368]. Similar to miR-26a, an angiogenesis-modulating effect was also observed in the case of miR-200b, which is upregulated in an TNF-α-dependent manner in diabetic mice, resulting in impaired angiogenesis [369], and possibly also altered expression of fibrillary collagens and fibronectin, as discussed above. Moreover, miR-155, is induced in wounds of diabetic mice, and its deficiency resulted in improved wound closure in knockout mice [301]. Apart from the identified targets BCL6, FIZZ1, RhoA, and SHIP1 it is noteworthy that miR-155 has also been linked to heparanase function [304], and is known to influence the proteolytic milieu via regulation of MMP-2 and TIMP-1 [303], which may have additionally influenced wound repair. Moreover, members of the miR-99 family are downregulated in diabetic wounds and may contribute to delayed repair via altering expression of several integrins or the PI3K/Akt signaling pathway, as discussed above [313-315]. Finally, inhibition of miR-146a in cultured human diabetic corneas was shown to have a beneficial effect on wound repair [236], however, it remains to be shown that its property of inhibiting fibronectin expression in tissues of diabetic animals [274] is linked to this phenomenon. miR-27b has been shown to target the matricellular proteins thrombospondin-1 and thrombospondin-2, which are important modulators of angiogenesis [370, 371]. In the context of diabetic wound repair and angiogenesis, it was shown that miR-27b upregulation in bone marrow-derived angiogenic cells promotes proliferation and survival, as well as tube formation, whereas therapeutic delivery of such miR-27b overexpressing into the wounds of diabetic mice improved wound repair [371]. Overall, these data confirm a role for ECM-targeting of

miRNAs in diabetic wound repair complications, however, several potential targets with known functions in repair still need to be experimentally confirmed.

Another area of tissue repair for which aberrant ECM regulation is a contributing factor is cardiac repair. Indeed, aberrant expression of syndecans, thrombospondins and MMPs, as well as altered fibrogenesis play major roles on this complex process [16, 134, 372]. With respect to altered miRNA dependent ECM regulation in myocardial infarction, both a direct impact on ECM synthesis and on proteolytic remodeling have been observed. Following the observation that the miR-29 family is dysregulated in myocardial infarction and targets numerous mRNAs encoding ECM proteins involved in cardiac fibrosis, van Rooij and coworkers demonstrated that miR-29 downregulation with anti-miRs in vitro and *in vivo* induces the expression of multiple collagens, whereas its over-expression in fibroblasts had the opposite effect [373]. Another miRNA, miR-24, was downregulated upon myocardial infarction in a rodent model, and its expression change was closely related to ECM remodeling [374]. Notably, in this study, lentivirus-mediated intramyocardial delivery of miR-24 improved heart function and attenuated fibrosis in the infarct border zone *in vivo*, which was ascribed to a targeting of the TGF-β processing enzyme furin, which in turn affected TGF-β-mediated ECM biosynthesis. Another *in vivo* study demonstrated that TGF-β1 and miR-21 were upregulated, whereas the inhibitor of TGF-β1-signaling, TGFβRIII was downregulated in the border zone of mouse hearts in response to myocardial infarction [375]. Importantly, miR-21 transfection into cardiac fibroblasts reduced TGF-βRIII expression and consequently increased collagen content. The authors demonstrated the presence of a reciprocal loop between miR-21 and TGF-βRIII in cardiac fibrosis in mice, and suggested targeting of this pathway as a novel new strategy for the prevention and treatment of myocardial remodeling [375].

Apart from regulating collagen expression, modulation of the proteolytic environment by miRNAs plays a role in cardiac remodeling. For example, in an ischemia-reperfusion model, miR-21 was shown to affect cardiac remodeling via upregulation of MMP-2 in a PTEN-dependent manner [376]. An increase in MMP-2 and MMP-9 activity was also observed in a mouse model, in which HMGB1 was injected in the peri-infarcted region of mouse failing hearts following coronary artery ligation. Notably, the authors found that HMGB1 upregulated miR-206, which in turn targeted the endogenous protease inhibitor TIMP-3, resulting in increased collagenolytic activity, enhanced left ventricular function and attenuated remodeling. Likewise, miR-17 was found to be upregulated in hearts of rodents subjected to myocardial infarction, and shown to 3' UTR of TIMP-2 and the protein-coding region of TIMP-1, thus promoting proteolysis in the infarcted tissue [377]. In a preclinical therapeutic approach, the authors could demonstrate that *in vivo* antago-miR treatment inhibiting miR-17 enhanced TIMP-1 and TIMP-2

expression, decreased MMP9 activity, reduced infarct size and improved cardiac function, suggesting miR-17 inhibition as a promising ECM-targeted approach for cardiac repair. Finally, miR-214 exerts a beneficial effect on cardiac remodeling, as it was shown that this miRNA increased the expression of collagen type I and III, of TGF-β1 and TIMP-1, whereas MMP-1 expression was decreased in cardiac fibroblasts subjected to AngII treatment [378]. These findings were corroborated in an *in vivo* model utilizing adenovirus-mediated delivery of miR-214. In summary, we conclude that there is strong evidence for a functional role of miRNA-mediated ECM remodeling in cardiac repair, and data in preclinical models show the therapeutic potential of miRNA and anti-miR-delivery in this setting.

Novel therapeutic approaches: miRNA delivery strategies

It is well established that miRNAs directly or indirectly regulate the expression and activity of ECM components. Recent data from our research group revealed that estrogen receptor β (ERβ) inversely regulates miR-10b and miR-145 expression in breast cancer cells. These miRNAs are critical modulators of the basic functional properties and the expression of ECM components in ERβ suppressed MDA-MB-231 breast cancer cells [379, 380]. These data imply that the efforts of miRNA targeting through ECM regulation must be more intense in order to manipulate the progression of various diseases. Recent advances in nanomedicine applied in several diseases contribute to overcome the limitations of the current therapeutic approaches. The markedly increased surface area of nanoparticles (NPs) in relation to their mass, surface reactivity and insolubility, the ability to agglomerate or change size in different media and enhanced endurance over conventional-scale substances, are some of their properties that make them attractive systems for several applications [381-384]. Since miRNAs have been identified as powerful mediators of wound healing , they are attractive candidates for a broad set of novel therapeutic strategies [385].

Depending on the mRNA-target miRNAs act either as gene suppressors or as inducers of miRNA expression. Therefore, in order to manipulate miRNA functions two targeting mechanisms have been developed: the pharmacologically active and synthetic double-strand miRNA mimics that restore miRNA expression and the oligonucleotide inhibitors or antago-miRs (known as anti-miRNAs) [386, 387]. Some of miRNAs characteristics include their small size, the known and conserved nucleotide sequence and the fact that one miRNA targets several mRNAs of a signaling pathway resulting in gene expression changes of its downstream targets in several biological processes. By this way, miRNAs act either as therapeutic agents or as therapeutic targets [388]. During their covalent conjugation with their carrier the cargo is released in the target cell through hydrolysis or reduction. This delivery system is very stable

and can protect the miRNA in the bloodstream. The greatest advantage of miRNA therapy is the high biological half-lives of miRNA mimics or anti-miRs inside the cells, providing their functions even when they are absent for the plasma [389, 390]. These advantages of miRNA applications led to the definition of a new class of drug targets and introduced miRNA therapy as the future challenge for clinical applications. Viral vehicles show higher efficiency to of incorporating miRNAs, since they have been designed to provide improved transfection efficiency miRNA-mimics or anti-miRNAs. However, they are characterized by increased cytotoxicity and immune response [391]. On the other hand, non-viral miRNA delivery systems are characterized by lower toxicity and immunogenicity, increased cellular uptake, water solubility, resistance to endonucleases, and phagocytosis [385, 387]. Several non-viral delivery strategies, including lipid-based, polymer-based and inorganic miRNA vesicles, have been designed and are widely used in targeting approaches [392].

Polymer-based delivery systems have been extensively utilized as miRNA carrier and are based on the conjugation of the miRNA phosphate groups with the amine groups of cationic polymers, therefore protecting nucleic acids from degradation. Synthetic polymeric carriers include poly(lactic-co-glycolic acid) (PLGA), cell-penetrating peptide (CPP), poly (amidoamine) (PAMAM), polyethylenimine (PEI) and chitosan as delivery vectors [392, 393]. Conjugation with hydrophilic polyethylene glycol (PEG) could increase the conjugation efficacy and improve the half-live of the vehicle in serum [394]. Targeted delivery of anti-miR-21 and anti-miR-10b PLGA-PEG polymer NPs reduced tumor growth in a breast cancer cell model *in vivo* [395]. Moreover, PLGA-based polyplexes, encapsulated miR-26a with improved efficiency, which significantly increased the bone-healing capacity in an osteoporosis model [396], implying the importance of this nanocarrier in tissue engineering applications. miR-146 PEI-NPs inhibited the expression of pro-fibrotic and inflammatory signaling molecules, thus attenuating renal fibrosis *in vivo* [397]. Moreover, HA-based PLGA/PEI miR-145 nanocarrier facilitates cellular uptake and enhance miR-145 expression in colon cancer cells that was followed by a reduction of tumor progression *in vitro* [398].

Synthetic cationic liposomes are lipid-based nucleic acid delivery vehicles, widely used as carriers due to the encapsulation and intracellular dissolution of the miRNA cargo with increased efficiency and reduced off-target effects. The anionic miRNAs conjugated with the cationic liposome generates a net charge that can easily penetrate the cell membrane via endocytosis, allowing the miRNA mimic or anti-miRNA to target several mRNAs and manipulate their expression, thus achieving efficient cellular uptake [399]. For instance, miR-126 that promotes angiogenesis *in vitro*, has been loaded to polyethylene glycol-modified liposomes forming the so called bubble liposomes, and its systemic delivery to an

ischemic fibrosis model resulted in the induction of the angiogenic factor VEGF and the improvement of blood flow [400]. A broad set of cationic lipososome miRNA nanocarriers have been designed and are extensively utilized in clinical applications. These include Lipofectamine (Invitrogen), DharmaFECT (Dharmacon), RNAi-MAX (Invitrogen), SilentFECT (Bio-Rad) and SiPORT (Invitrogen). The significance of their use is that these liposome formulations are biodegradable, bio-compatible, they have increased affinity to the cell surface and are non-pathogenic and non-immunogenic. The miRNA is released in the cytoplasm following intracellular dissolution of the particle [401].

Inorganic systems for delivering miRNAs have been developed since they exert high stability *in vivo*, antimicrobial properties, biocompatibility and low levels of cytotoxicity. These include gold NPs (AuNPs), silica NPs and Fe_3O_4-based NPs. An interesting example of AuNPs in a tissue regeneration application is their conjugation with the negatively-charged miR-29b, which resulted in improved efficiency of miR-29b to enter the cytoplasm and regulate osteogenesis, in low doses [402]. Another approach involves the conjugation of a nucleic acid to the Fab fragments of a cell-specific antibody. Antibodies are attractive vehicles for targeted delivery of miRNAs *in vivo*, since they exert high affinity and binding specificity [403, 404]. Nonetheless, in order to design a safe and efficient miRNA nanocarrier some concerns must be considered [403]. The most important issue is the anatomy of the targeted organ, however, the therapeutic dose, the tissue microenvironment and the ECM composition of each cell type must be evaluated in order to improve the therapeutic potential of the mimic miRNA or the anti-miRNA. Several miRNA nanocarriers for targeted therapy of fibrotic diseases have reached clinical development [386, 405]. The first miRNA nanocarrier that entered phase I clinical trials was a miR-34 mimic conjugated to liposomes (MRX34) for the treatment of multiple solid tumors (NCT01829971). EDV™ nanocells constitutes a novel delivery system for malignant pleural mesothelioma and non-small cell lung cancer treatment, which includes the intravenously administered EGFR (Vectibix® Sequence)-Targeted EnGeneIC Dream Vectors Containing miR-16 mimic (NCT02766699). Regarding wound healing in diabetic patients, the role miR-200b and miR-21 mimics will be evaluated in clinical trials (NCT02581098). The role of anti-miR-122 in chronic hepatic fibrosis (hepatitis C) is currently evaluated in different phase II clinical trials (NCT01646489, NCT01200420, NCT01872936, NCT02031133, NCT02508090). Finally, the impact of GalNAc-conjugated antimiR-103/107 on patients with type 2 diabetes and non-alcoholic fatty liver diseases is evaluated in ongoing clinical trials (NCT02612662, NCT02826525).

The novel nanosystems for miRNA delivery and the subsequent ECM manipulation are a major challenge for novel therapeutic approaches and they may improve the design and development of safe

and efficient miRNA carriers, which will serve in the diagnosis and therapeutic strategies to attenuate the progression of various diseases, including wound healing.

Concluding remarks

ECM is a highly orchestrated, dynamic network of non-cellular macromolecules that provide tissues and organs with structural stability and functionality. Apart from its role as scaffold of cells, ECM components dynamically interact to maintain cellular phenotype, thus serving as critical modulators of basic functional properties, such as proliferation, migration, angiogenesis and differentiation. Wound healing is an essential process of the proper tissue functioning and it is consisted of four distinct phases including hemostatic, inflammatory, proliferative and tissue remodeling phase. Despite the fact that wound healing is a strictly structured process, its de-regulation may result in the development of chronic wounds often associated with other comorbidities, including diabetes and the development of fibrosis and hypertrophic scars. An abundance of evidence has shown that epigenetic modifications participate in the regulation of this complex and systematic response. miRNAs are implicated in all wound healing phases through their direct or indirect interactions with ECM components, therefore they could be considered as mediators of this response. In recent years, several attempts for targeting miRNAs have been conducted in order to systematically deliver miRNAs in specific cell types and tissues. miRNA delivery via viral vehicles, synthetic polymer carriers, synthetic cationic liposomes and inorganic nanocarriers has yielded promising results in preclinical disease models, and several clinical trials for miRNA delivery have been initiated. The development of these delivery concepts may further develop the established clinical applications for patient management as well as the diagnosis and treatment of several diseases.

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Declaration of interest

The authors state no conflict of interest.

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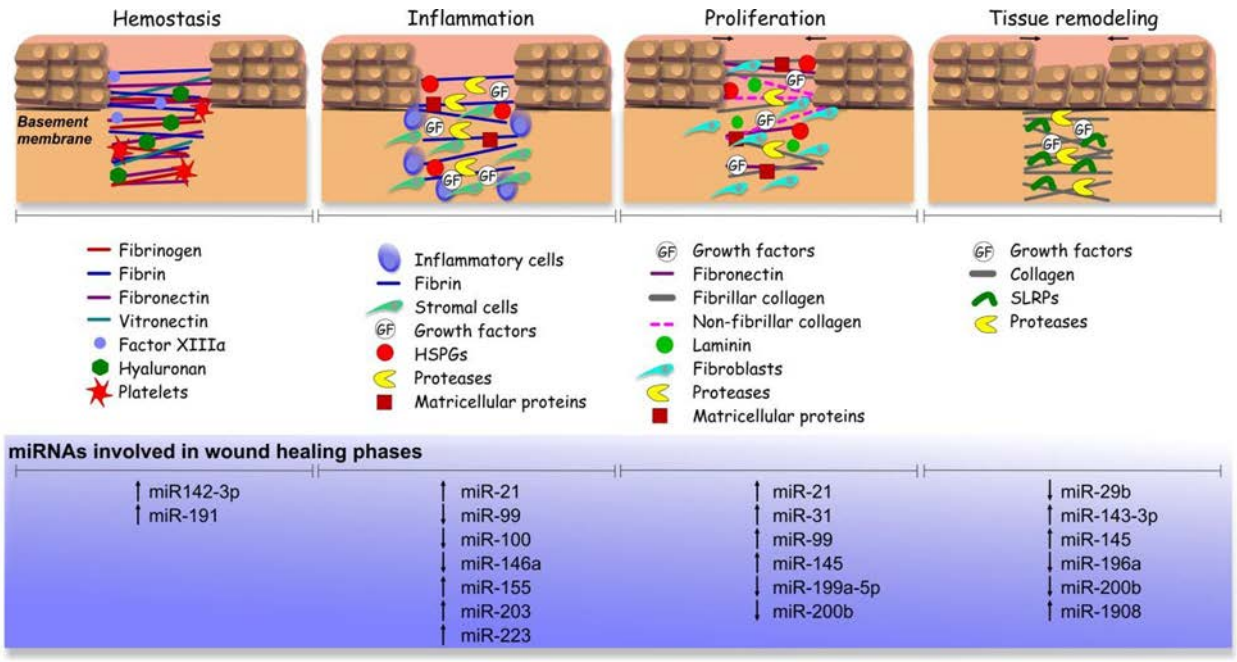
Figures Legends

Figure 1. Schematic representation of wound healing phases. In each phase, the participation of ECM proteins is essential and its composition, mainly in the connective tissue, alters the hemostatic, inflammatory, proliferative and tissue remodeling phases of healing. Fibrin, fibronectin, platelets and HA bound to fibrinogen, vitronectin, factor XIIIα and other clotting proteins are major constituents during the hemostatic phase of the wound. As leukocytes migrate into the wound site, they release proteases to degrade the fibrin-rich ECM. Immune cells secrete a broad range of inflammatory cytokines and growth factors to attract stromal cells to migrate into the wound. Several matrix-stored growth factors (i.e. PDGF, EGF, TGF-β) and PGs released and secreted from endothelial cells (i.e. syndecans, decorin, lumican) are also displaced. In the next phase, stromal fibroblasts migrating into the wound area (arrows) produce a provisional ECM characterized by the presence of fibronectin, matricellular proteins, decreased protease activity, fibrillar (type I, III) and non-fibrillar (type IV, VI, VII) collagen, and growth factors (i.e. EGF, FGF, TGF-β). The secreted matrix PGs (i.e. decorin, lumican) and collagen that are associated with mature healing wounds are secreted by keratinocytes and leukocytes to promote proliferation and migration of vascular components, endothelial and epithelial cells. During the tissue remodeling phase, the stiffer matrix and several growth factors (i.e. TGF-β) trigger stromal cells to induce wound contraction by adopting a myofibroblast phenotype. The supportive ECM is enriched in matrix PGs, proteases and realigned collagen type I cross-linked fibers. The final step in wound repair involves the formation of overly aligned collagen fibers that regain almost 80% of the primary tissue functionality. The lower panel demonstrates a summary of the most critical miRNAs that are involved in each wound healing phase and manipulate crucial cell functions, such as fibrillogenesis in the connective tissue, proliferation, migration, angiogenesis and tissue remodeling. Arrows indicate up- or downregulation of miRNA expression.

Figure 2. The canonical mechanism of miRNA biogenesis and post-transcriptional gene silencing. The initiation step is the formation of 70-nucleotide pri-miRNA by the RNA polymerase II and III in the nucleus. Pri-miRNA is cleaved by the Drosha complex and the resulting pre-miRNA, which has a short stem plus a ~2-nucleotide 3' overhang is recognized by the exportin-5 complex and is exported to the cytoplasm, where it is cleaved by the Dicer complex to the mature miRNA duplex. The miRNA passenger strand is degraded and the mature miRNA strand (17-25 nucleotides), together with Argonaute proteins (Ago2) guides the RISC to bind the 3’ UTR region of the target mRNA. Depending on the

complementarity of the seed sequence of the miRNA and its cognate mRNA, miRNA binding to the 3' UTR site destabilizes the mRNA-target. This process may result in mRNA degradation, translational repression or mRNA deadenylation (not shown). Novel delivery strategies involve the encapsulation of miRNA nucleic acids (mimics or anti-miRs) into bio-degradable liposome formations, which are characterized by improved stability, high affinity, and low toxicity. These nanocarriers may serve as diagnostic tools and therapeutic strategies in several clinical applications.

Figure 3. miRNA-mediated ECM targeting is a critical regulator of basic functional properties, such as cell proliferation, differentiation, migration and survival. The production of pri-miRNA in the nucleus is followed by its export to the cytoplasm and its further cleavage to the mature miRNA, which targets specific mRNAs. Here, representative examples of functional relationship between miRNAs and major ECM components participating in wound healing are shown.


Hemostasis
Inflammation
Proliferation
Tissue remodeling
Basement membrane
GF
Fibrinogen
Fibrin
Fibronectin
Vitronectin
Factor XIIIa
Hyaluronan
Platelets
Inflammatory cells
Fibrin
Stromal cells
Growth factors
HSPGs
Proteases
Matricellular proteins
Growth factors
Fibronectin
Fibrillar collagen
Non-fibrillar collagen
Laminin
Fibroblasts
Proteases
Matricellular proteins
Growth factors
Collagen
SLRPs
Proteases
miRNAs involved in wound healing phases
↑ miR142-3p
↑ miR-191
↑ miR-21
↓ miR-99
↓ miR-100
↓ miR-146a
↑ miR-155
↑ miR-203
↑ miR-223
↑ miR-21
↑ miR-31
↑ miR-99
↑ miR-145
↓ miR-199a-5p
↓ miR-200b
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↑ miR-143-3p
↑ miR-145
↓ miR-196a
↓ miR-200b
↑ miR-1908

Figure 1

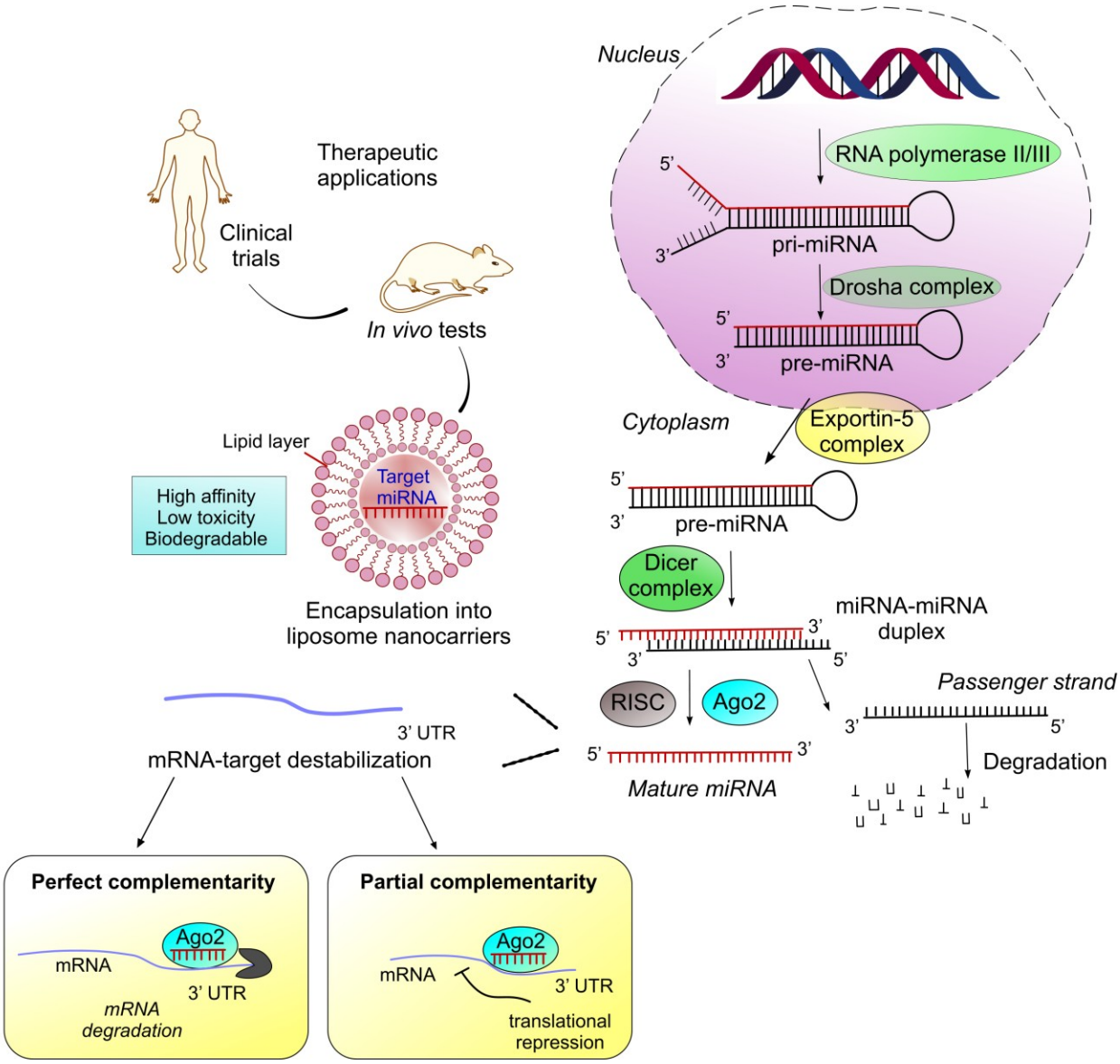
Nucleus
RNA polymerase II/III
5'
3'
pri-miRNA
Drosha complex
5'
3'
pre-miRNA
Cytoplasm
Exportin-5 complex
5'
3'
pre-miRNA
Dicer complex
miRNA-miRNA duplex
5'
3'
3'
5'
RISC
Ago2
Passenger strand
3'
5'
Degradation
5'
3'
Mature miRNA
Therapeutic applications
Clinical trials
In vivo tests
Lipid layer
Target miRNA
High affinity
Low toxicity
Biodegradable
Encapsulation into liposome nanocarriers
3' UTR
mRNA-target destabilization
Perfect complementarity
Ago2
mRNA
3' UTR
mRNA degradation
Partial complementarity
Ago2
mRNA
3' UTR
translational repression

Figure 2

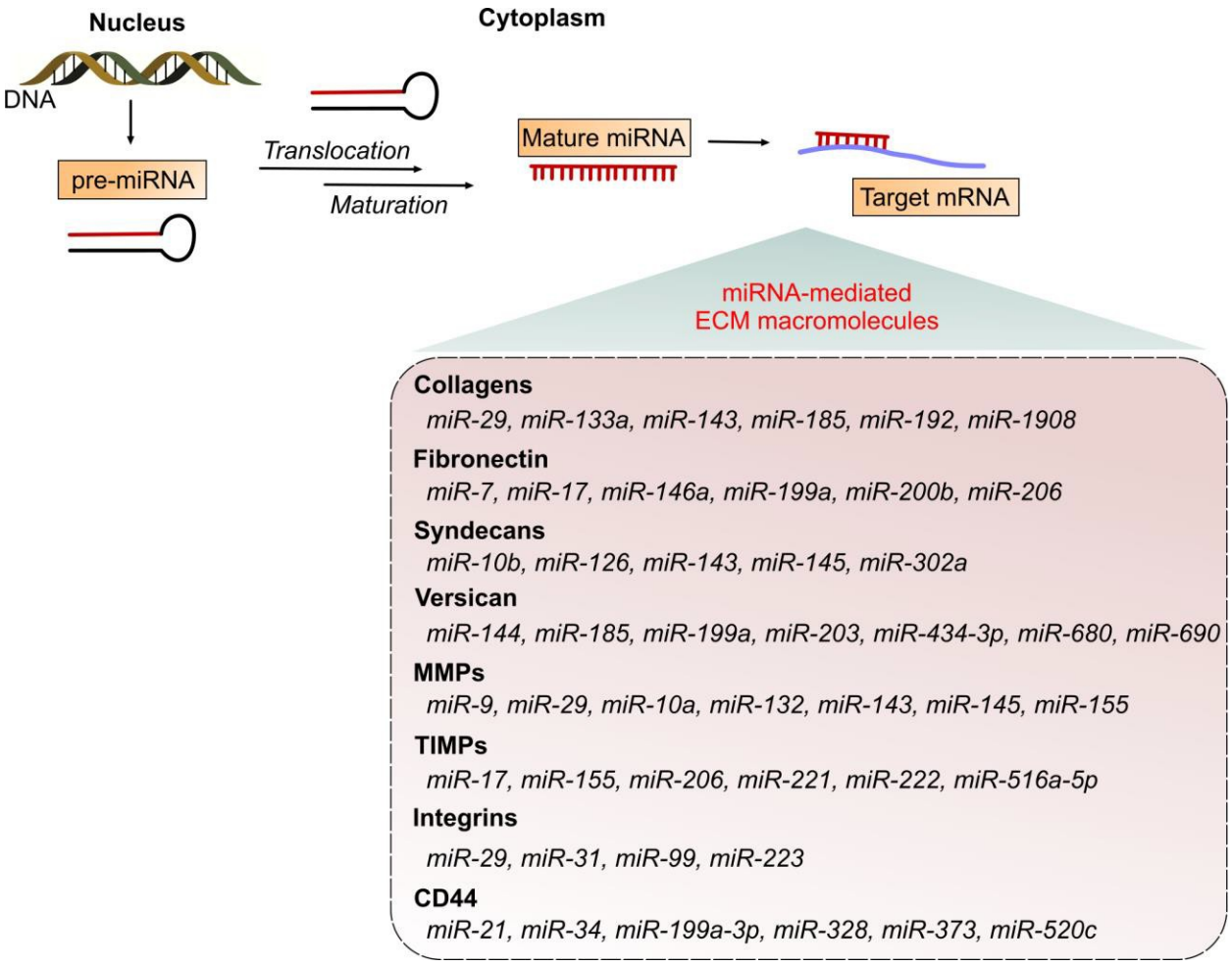
Nucleus
Cytoplasm
DNA
pre-miRNA
Translocation
Maturation
Mature miRNA
Target mRNA
miRNA-mediated
ECM macromolecules
Collagens
miR-29, miR-133a, miR-143, miR-185, miR-192, miR-1908
Fibronectin
miR-7, miR-17, miR-146a, miR-199a, miR-200b, miR-206
Syndecans
miR-10b, miR-126, miR-143, miR-145, miR-302a
Versican
miR-144, miR-185, miR-199a, miR-203, miR-434-3p, miR-680, miR-690
MMPs
miR-9, miR-29, miR-10a, miR-132, miR-143, miR-145, miR-155
TIMPs
miR-17, miR-155, miR-206, miR-221, miR-222, miR-516a-5p
Integrins
miR-29, miR-31, miR-99, miR-223
CD44
miR-21, miR-34, miR-199a-3p, miR-328, miR-373, miR-520c

Figure 3

Table 1. Targets and main actions of major miRNAs linked to wound healing and fibrosis in clinical indications.

microRNA	*Predicted Targets*	*Putative Action(s)*	*Effect*	*References*
let-7d	HMGA2, TGFβ/SMAD3	Attenuates EMT *in vitro* & *in vivo*; reverses fibrotic phenotype (pulmonary fibrosis)	Anti-fibrotic	[213-215]
miR-10b	PTEN, HOXD10	Mediates TGF-β-dependent EMT (myocardial & skin fibrosis)	Anti-fibrotic	[216, 217]
miR-21	EGR3, vinculin, LepR, TGFβ/SMAD7	Fibroblast migration; delay in epithelialization in acute human skin wounds (skin fibrosis); mediates fibrogenic activation (pulmonary fibrosis)	Pro-fibrotic	[198, 199, 218]
miR-29	Collagen I & IV, PDGF, TGFβ1/SMAD2/SMAD3, fibrillin, elastin, profibrotic genes, Wnt/ Frizzled/ β-catenin, PI3K/AKT, αSMA, fibronectin, ITGB1, IGF-I, PDGFR-β, TGFβ1/ PI3K/AKT, TNF-α/NF-κB	Antifibrotic function in cardiac fibroblasts (cardiac fibrosis); negatively related to the severity of the fibrosis in human fetal lung fibroblast (pulmonary fibrosis); antifibrinogenic mediator through the inhibition of collagen I&IV expression, induced by TGFβ1, and its deposition in the liver (kidney & hepatic fibrosis); high glucose or TGFβ stimulation downregulates miR-29 expression and promotes collagen formation (renal fibrosis)	Anti-fibrotic	[219-227]
miR-30a	TET1, Snai1	Decrease in the degree of myocardial fibrosis (cardiac fibrosis); blocks mitochondrial fission (pulmonary fibrosis); EMT inhibition *in vitro* & *in vivo* (diabetic & peritoneal fibrosis)	Anti-fibrotic	[228-231]

miR-203	Ran, Raph1	Pro-proliferative and pro-migratory factor in cutaneous wound healing; suppresses hepatic fibrosis	Anti-fibrotic	[212, 243]
miR-130a-3p	LepR, PPARγ,	Delayed epithelialization in an acute human skin wound model (skin fibrosis); mediator of macrophage's fibrogenesis	Anti-fibrotic	[198, 204]
miR-142-5p	SOCS1/STAT6	Regulates macrophage profibrogenic gene expression in chronic inflammation via IL-4/ IL-13 mediation	Pro-fibrotic	[204]
miR-145	TNFRSF11B, KLF4	Inhibits cell proliferation and fibrosis (articular fibrosis); promotes fibroblast trans-differentiation (pulmonary fibrosis); TGF-β1-stimulated myofibroblast differentiation & activation (corneal fibrosis)	Anti-fibrotic	[232-234]
miR-146a	αSMA, SMAD4	Represses pro-inflammatory cytokines within the wound (corneal fibrosis); negatively regulates the osteogenesis and bone regeneration *in vitro* & *in vivo*	Anti-fibrotic	[235-237]
miR-181α	PHLPP2	Enhanced keloid fibroblast DNA synthesis and proliferation and inhibited apoptosis (skin fibrosis)	Pro-fibrotic	[238]
miR-181-5p	STAT3, Bcl2	Activation of autophagy (liver fibrosis)	Anti-fibrotic	[239]
miR-200	TGFβ2, ZEB1/2	Decreases TGF-β signaling and TGF-β-dependent EMT (liver & renal fibrosis)	Anti-fibrotic	[240-242]

miR-214-5p	CTGF, TGFβ	Increased MMP2, MMP9 expression levels; hepatitis-C induced liver fibrosis; hepatic remodeling (liver fibrosis)	Anti-fibrotic	[244-246]
miR-483-3p	Cell proliferation protein MKi76, the kinase MK2 and a transcription factor YAP1	Control keratinocyte proliferation, growth arrest during re-epithelialization, promotion of wound healing *in vitro* & *in vivo*	Anti-fibrotic	[211]

Abbreviations: Bcl2, B-cell lymphoma 2; Col1A1, collagen type I alpha 1; Col3A1, collagen type III alpha 1; Col4A1, collagen type IV alpha 1; EGR, early growth response factor; EMT, epithelial-to-mesenchymal transition; HMGA2, high-mobility group AT-hook 2; IGF-I, insulin-like growth factor I; ITGB1, integrin β1; KLF4, Kruppel-like factor 4; LepR, leptin receptor; MMP, matrix metalloproteinase; PDGFR, platelet-derived growth factor receptor; PHLPP2, PH domain leucine-rich repeat protein phosphatase 2; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor γ; PTEN, phosphatase and tensin homolog deleted on chromosome 10; Ran, Ras-related Nuclear protein; Raph1, Ras-associated and pleckstrin homology domains-containing protein 1; αSMA, alpha smooth muscle actin; SMAD, mothers against decapentaplegic homolog; Snai1, snail family transcriptional repressor 1; SOCS1, suppressor of cytokine signalling 1; STAT6, signal transducer and activator of transcription 6; TGF, transforming growth factor; TET1, ten-eleven translocation 1; TNF-α, tumor necrosis factor alpha; TNFRSF11B, tumor necrosis factor receptor superfamily member 11b

Highlights

- Extracellular matrix (ECM) plays regulatory roles in cell functions, tissue regeneration and remodeling.
- The interplay between ECM and resident cells exerts its critical role in many aspects of wound healing, matrix degradation and biosynthesis.
- Epigenetic regulatory mechanisms, such as the endogenous non-coding microRNAs (miRNAs) drive the wound healing response and dermal regeneration.
- miRNAs have pivotal roles in ECM composition (matrix proteins, proteoglycans and proteases) during wound healing, serving themselves as target biomarkers for systematic regulation of wound repair.
- miRNAs targeting and the delivery strategies designed for clinical applications are emerging areas of research with clinical relevance.