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Review

MicroRNA-dependent targeting of the extracellular matrix as a mechanism of regulating cell behavior ☆

Sherif Abdelaziz Ibrahim [a,*], Hebatallah Hassan [a], Martin Götte [b,**]

[a] Department of Zoology, Faculty of Science, Cairo University, Giza 12613, Egypt
[b] Department of Gynecology and Obstetrics, Münster University Hospital, Albert-Schweitzer-Campus 1, D11, 48149 Münster, Germany

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ABSTRACT

Background: MicroRNAs are small noncoding RNAs which regulate gene expression at the posttranscriptional level by inducing mRNA degradation or translational repression. MicroRNA-dependent modulation of the extracellular matrix and its cellular receptors has emerged as a novel mechanism of regulating numerous matrix-dependent processes, including cell proliferation and apoptosis, cell adhesion and migration, cell differentiation and stem cell properties.
Scope of review: In this review, we will present different mechanisms by which microRNAs and extracellular matrix constituents mutually regulate their expression, and we will demonstrate how these expression changes affect cell behavior. We will also highlight the importance of dysregulated matrix-related microRNA expression for the pathogenesis of inflammatory and malignant disease, and discuss the potential for diagnostic and therapeutic applications.
Major conclusions: MicroRNAs and matrix-dependent signal transduction processes form novel regulatory circuits, which profoundly affect cell behavior. As misexpression of microRNAs targeting extracellular matrix constituents is observed in a variety of diseases, a pharmacological intervention with these processes has therapeutic potential, as successfully demonstrated in vitro and in advanced animal models. However, a deeper mechanistic understanding is required to address potential side effects prior to clinical applications in humans.
General significance: A full understanding of the role and function of microRNA-dependent regulation of the extracellular matrix may lead to new targeted therapies and new diagnostics for malignant and inflammatory diseases in humans. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

1. Introduction

1.1. MicroRNAs and the extracellular matrix — a bidirectional relationship

MicroRNAs (miRNAs) are small non-coding RNA molecules consisting of 19–24 nucleotides, which have emerged as potent posttranscriptional regulators of a wide range of cellular processes [1–2]. Via sequence-specific binding to cognate mRNAs, miRNAs can trigger a cellular program that leads to either degradation or translational repression of that mRNA, or, in more rare cases, to an upregulation of gene expression (see Section 1.2). Considering this mode of action, it is conceivable that the vast majority of cellular and extracellular functions are potentially regulated by miRNAs either directly or indirectly. In this review, we will find numerous examples for a regulation of extracellular matrix (ECM) constituents and of their cellular receptors by miRNAs, and we will learn how miRNA-dependent ECM regulation affects key cellular processes, including cell proliferation, survival and apoptosis, cell adhesion and migration, stemness and cell differentiation. Notably, the regulatory relationship between miRNAs and the ECM is far from being unidirectional, as the ECM in the cellular microenvironment is known to influence numerous signaling processes which can in turn influence miRNA expression [4–6].

Price et al. [7] compared the miRNA expression patterns of five epithelial cancer cell lines grown either on plastic or the basement-membrane-like Matrigel matrix, which contains laminin, collagen IV, entactin and perlecan as major constituents. The authors identified up-regulated miR-1290 and miR-210 and down-regulated miR-29b and miR-32 as a Matrigel-associated miRNA signature, and underscored their functional significance by demonstrating changes in colon cancer cell adhesion, proliferation and invasion upon experimental modulation

Abbreviations: ceRNA, competing endogenous RNA; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; FAK, focal adhesion kinase; FGF, fibroblast growth factor; HS, Heparan sulfate; HSPG2, heparan sulfate proteoglycan 2, perlecan; IL, interleukin; LDL, Low density lipoprotein; miRNA, microRNA; MMP, matrix metalloproteinase; NDST1, N-deacetylase/N-sulfotransferase-1; NF-κB, nuclear factor-κB; PAI-1, plasminogen activator inhibitor-1; SMC, Smooth muscle cell; SNP, single nucleotide polymorphism; SPARC, Secreted protein acidic and rich in cysteine; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; uPAR, urokinase-type plasminogen activator receptor; UTR, untranslated region; VEGF, vascular endothelial growth factor

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* Corresponding author. Tel.: +20 2335676689.
** Corresponding author. Tel.: +49 2518356117.
E-mail addresses: sheriefabdelaziz@yahoo.com (S.A. Ibrahim), martingotte@uni-muenster.de (M. Götte).

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of these miRNAs. While this study did not allow to distinguish between the impact of different matrix constituents, two independent studies identified the interaction between the extracellular glycosaminoglycan hyaluronan and its cell surface receptor CD44 as an important signaling element modulating the expression of miR-21: In glioma cells lacking functional tumor suppressor PTEN, hyaluronan-mediated overexpression of miR-21 resulted in subsequent downregulation of Spry2 protein, a negative regulator of malignant progression and invasiveness [8]. In breast cancer cells, hyaluronan–CD44 interaction resulted in miR-21 upregulation mediated by the stemness-associated transcription factor Nanog, and a subsequent targeting of gene products associated with apoptosis and chemotherapy sensitization [9]. These examples clearly demonstrate the bidirectional relationship between ECM-mediated signaling events, and miRNA-dependent regulation of ECM composition. Before we explore these aspects in more depth, we will familiarize ourselves with the basic molecular biology of miRNAs.

1.2. A primer on microRNAs

Historically, the first miRNA was discovered in the worm *Caenorhabiditis elegans* in 1993, where a 22 nucleotide non-coding, hairpin shaped RNA encoded by the lin-4 gene was demonstrated to bind to and suppress the translation of LIN14 mRNA [10,11]. Currently, over 2500 mature human miRNAs are known according to the latest release of miRbase (mirbase.org; 20.0, June 2013) [12]. An overview of miRNA biogenesis is provided in Fig. 1. miRNAs are chromosomally encoded, and are initially transcribed in the nucleus by RNA polymerase II as large primary (pri)-miRNAs. Interestingly, the majority of miRNA encoding genes overlaps with defined transcriptional units, and may be coregulated with these [13]. The pri-miRNAs are subsequently processed by the RNase III endonuclease Drosha and the RNA binding protein Pasha/DGCR8 into ~70 nucleotide long stem-loop precursor (pre)-miRNAs. These pre-miRNAs are translocated to the cytoplasm by the nuclear pore constituent exportin 5, where they are processed by the RNase III-like enzyme Dicer into small transient ~22 nucleotide RNA duplexes [14,15]. These duplexes are further processed into single-stranded miRNAs by helicases, while the antisense strand (designated the '*-strand') is degraded. Mature miRNAs are incorporated into the RNA-induced silencing complex. Here, they assemble with their so-called 6–7 nucleotide 'seed sequence' located at the 5′-end of the miRNA to the complementary 3′-untranslated regions (UTRs) of mRNA. Via this mechanism, one miRNA can bind to a variety of target complementary mRNAs, causing regulation of gene expression usually via mRNA degradation or transcriptional inhibition [1,2] (Fig. 1). In some cases, the interaction of miRNAs with the 5′UTR of target genes results in upregulated gene expression [16,17]. Computer algorithms such as TargetScan and PicTar allow for the prediction of mRNAs potentially regulated by a particular miRNA and vice versa [18,19]. Consequently, public databases such as miRbase (www.mirbase.org), DIANA (http://diana.cslab.ece.ntua.gr/) or microRNA.org have become an essential tool in miRNA research. While miRNA genes can be individually regulated, some miRNAs form clusters, which can be transcribed as a single transcript (see [20] for discussion). At the same time, one mRNA UTR can

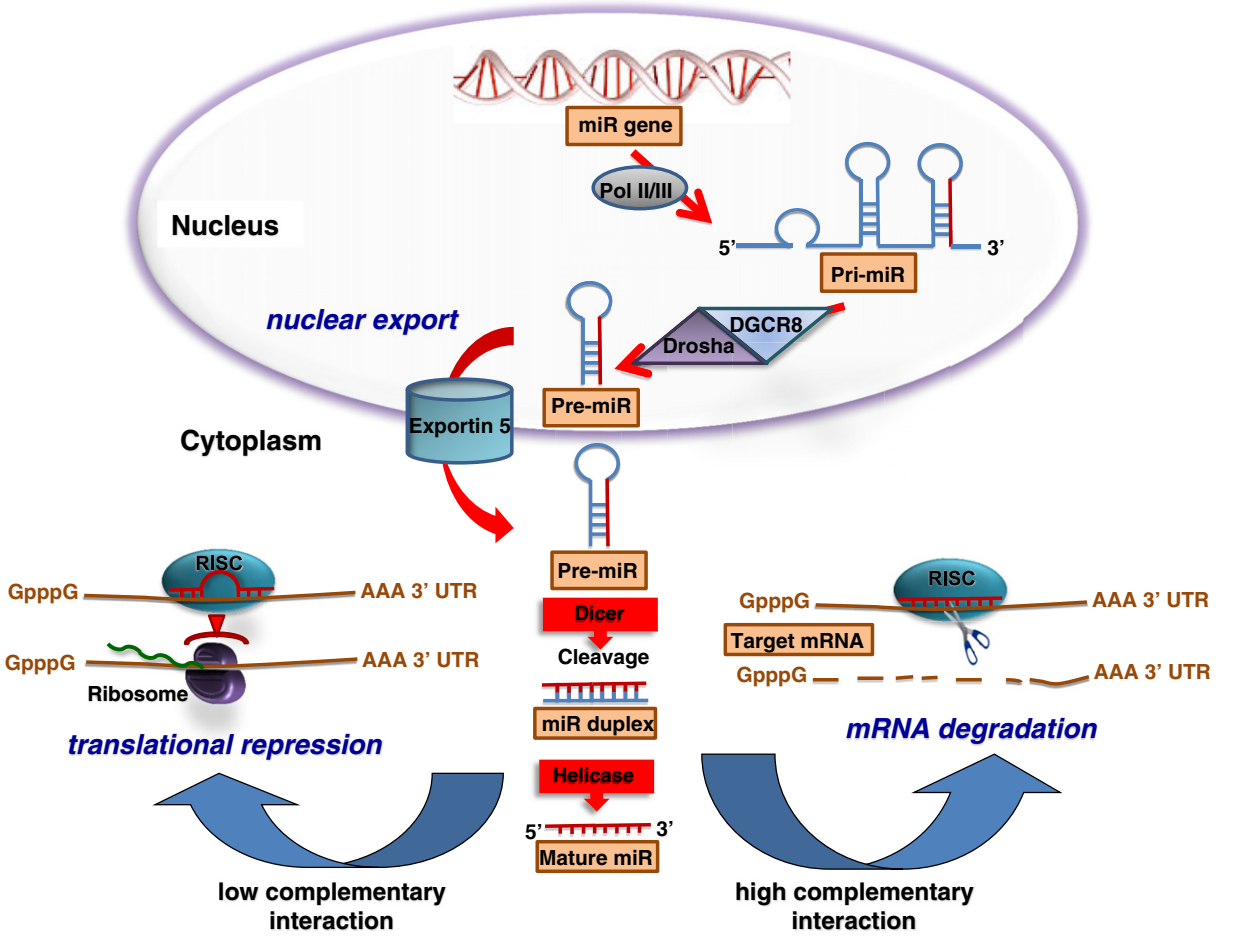

Fig. 1. Schematic representation of miRNA biogenesis and its mode of action. miRNAs are transcribed as pri-miRNAs by pol II/III, which are then processed via a complex (Drosha + DGCR8) forming pre-miRNA. Translocation of pre-miRNA from nucleus to cytoplasm is mediated by Exportin-5. Pre-miRNA is further cleaved by Dicer complex to give miRNA duplex, which is converted into mature miRNA. The functional strand of mature miRNA is then incorporated with Argonaute (Ago2) proteins into the RNA-induced silencing complex (RISC) to silence its target mRNAs through high complementarity resulting in the degradation of mRNA or low complementarity resulting in translational repression [1–3].

be controlled by different clusters or individual miRNAs [21]. The concerted action of coregulated miRNA gene clusters can amplify the regulatory effect on the target mRNA, and enables the formation of regulatory loops and networks [3,22]. Finally, miRNA expression is under epigenetic control, adding further to the regulatory complexity [23,24]. In the following section, we will discuss different modes by which miRNAs regulate the expression of ECM constituents, and how ECM-dependent signaling processes determine the expression of miRNAs. Additional modes of regulating ECM constituents, such as the regulation of matrix turnover by matrix metalloproteinases (MMPs) and protease inhibitors, and induction of matrix biosynthesis by miRNA-dependent cytokine expression have been recently reviewed [20], and will therefore be covered in less detail.

2. miRNAs and the ECM — modes of regulation

2.1. Direct targeting of ECM-related mRNAs by miRNAs

The classical regulatory mode of miRNAs towards their cognate target mRNAs involves a binding interaction of the miRNA seed sequence with the 3′UTR of the mRNA, triggering either mRNA degradation or translational inhibition (Fig. 1). In vitro, formal proof of this regulatory mechanism involves 3′UTR-dependent luciferase reporter assays in the presence or absence of a particular microRNA or a microRNA inhibitor. The use of mutant reporter constructs provides further information on the relevant base pairs for this interaction. This approach is not trivial, as not every predicted target sequence is actually involved in miRNA-dependent regulation. For example, among the 7464 predicted target sequences for human miR-145 (microRNA.org), only about 30 were regulated more than 1.5-fold at the mRNA level in a study on human MDA-MB-231 breast cancer cells supported by Affymetrix transcriptomic analysis [25]. While a regulation at the translational level will certainly expand the number of regulated targets, it appears unlikely that all of the several thousand predicted targets will be regulated. The importance for delivering formal proof of this mode of regulation was demonstrated in the case of glypican-3, a growth factor- and morphogen-binding cell surface proteoglycan involved in the pathogenesis of Simpson–Golabi–Behmel syndrome and hepatocellular carcinoma [26]: miR-96 and miR-182 contain the same seed region, and are thus both predicted to target complementary sequences in the short 3′ UTR of glypican-3. Using mutational analysis, Jalvy-Delvaille et al. [27] demonstrated that only miR-96, but not miR-182 is capable of inducing downregulation of glypican-3. This differential regulation was due to miRNA nucleotide 8, immediately downstream of the UUGGCA seed, which apparently played a critical role in target recognition. In this review, we will encounter numerous examples for the 3′UTR-based mode of direct miRNA regulation of ECM constituents. To demonstrate the regulatory impact of miRNA regulation on cellular behavior in the case of a single target, we will discuss the case of miR-10b-dependent regulation of the cell surface proteoglycan syndecan-1, which has pleiotropic ECM-associated roles, ranging from matrix receptor to modulator of integrin, MMP and heparanase function [28–30]. Initiated by the observation of an inverse correlation between expression of the prometastatic miR-10b and its predicted target syndecan-1 in clinical breast cancer specimens [31], Ibrahim et al. [32] could demonstrate the downregulation of syndecan-1 expression via miR-10b–3′UTR interactions in human breast cancer cell lines. Syndecan-1 depletion affected MDA-MB-231 breast cancer cell motility, invasiveness and resistance to radiotherapy [28,32]. At the cellular level, filopodia formation and adhesion to the large ECM glycoproteins fibronectin and laminin were increased in syndecan-1-depleted cells. Increased signaling via focal adhesion kinase (FAK) and Rho-GTPase pathways associated with ECM-induced integrin activation was identified as the underlying mechanistic principle. Thus, the study by Ibrahim et al. [32] demonstrated that miRNA regulation of a single ECM coreceptor could simultaneously affect multiple cellular processes relevant to the progression of malignant disease. In addition, miR-10b-mediated targeting of the transcription factor HOXD10 promotes upregulation of further proinvasive factors, including MMP-14 and urokinase-type plasminogen activator receptor (uPAR) [33,34], resulting in a strong synergistic prometastatic effect of miR-10b.

Not only can synthesis of proteoglycan core proteins be regulated by miRNAs, but also the structure of their glycosaminoglycan carbohydrate chains. In the case of N-deacetylase/N-sulfotransferase-1 (NDST1), an enzyme mediating early steps of heparan sulfate (HS) biosynthesis, its targeting by miR-24 reduced HS sulfation and thereby its binding affinity for the major angiogenesis factor vascular endothelial growth factor (VEGF)-A [35]. As a consequence, endothelial responses to VEGF-A were reduced. A recent study in the worm *C. elegans* provided further evidence for a role of miRNAs in regulating cell behavior via glycosaminoglycans. Pedersen et al. [36] demonstrated that miR-79, the ortholog of mammalian miR-9, controls two proteins in the proteoglycan biosynthetic pathway, a chondroitin synthase and a uridine 5′-diphosphate-sugar transporter. The resulting partial shutdown of HS biosynthesis resulted in a disruption of glypican-dependent neuronal migration and neurodevelopmental defects. Apart from HS, biosynthesis of another glycosaminoglycan and major constituent of interstitial matrices, hyaluronan, was shown to be potentially regulated by miRNAs. Inhibition of the miRNA let-7 resulted in upregulation of its target, hyaluronan synthase 2, thus potentiating survival, invasion and adhesion of human breast and cervical cancer cell lines [37]. However, as hyaluronan synthase 2 has also functions independent of hyaluronan biosynthesis [38], it remains to be shown which effects can be attributed to altered hyaluronan biosynthesis.

Not only matrix biosynthesis is subject to miRNA regulation, but also its degradation and remodeling [20]. We will discuss examples for miRNA-regulation of the MMP family of zinc-dependent endopeptidases, which are capable of degrading collagens, large matrix glycoproteins, extracellular proteoglycans and some matrix receptors [39], in Section 4. Matrix and cell surface HS can be degraded or structurally modified by the enzymes heparanase and SULF1/2, respectively [40–42]. The HS editing enzyme hSulf-1, which cleaves 6-O-sulfated residues from HS and thus influences binding of cytokines and morphogens, is targeted by miR-21 along with the tumor suppressor PTEN, resulting in increased pro-survival signaling, hepatocellular carcinoma proliferation and tumor growth in vivo [41]. In an animal model of gastric cancer, miR-516a-3p exerted an antimetastatic effect via Sulf-1 downregulation and an associated reduced activation of HS-dependent Wnt signaling [42]. These studies highlight context-dependent effects, and the influence of synchronous targeting of multiple mRNAs by a particular miRNA. The HS degrading endo-glycosidase heparanase has well-established roles in promoting cancer metastasis via basement membrane degradation, and in tumor angiogenesis via modulation of proangiogenic signaling and MMP expression [40,43]. An inverse correlation between the expression of miR-1258 and heparanase was noted in brain metastatic breast cancer cells, non-small cell lung cancer, and breast cancer, where miR-1258 expression was associated with negative prognostic parameters and reduced survival [44–46]. Notably, miR-1258-induced heparanase downregulation resulted in reduced cancer cell invasiveness and experimental metastasis in vitro and in vivo [45,46]. An overview of selected miRNAs directly regulating ECM constituents, their receptors, and their remodeling factors, as discussed in this review, is provided in Fig. 2 and Table 1.

2.2. Indirect regulation of ECM constituents via miRNA-dependent targeting of transcriptional activators and repressors

As pointed out earlier, miRNAs are mainly considered negative regulators of gene expression. However, in some instances, an upregulation of mRNA and protein expression is observed upon increasing miRNA expression [16,17,25]. This upregulation could in some cases be linked to a direct regulatory mechanism of miRNA interaction with the 5′-end of

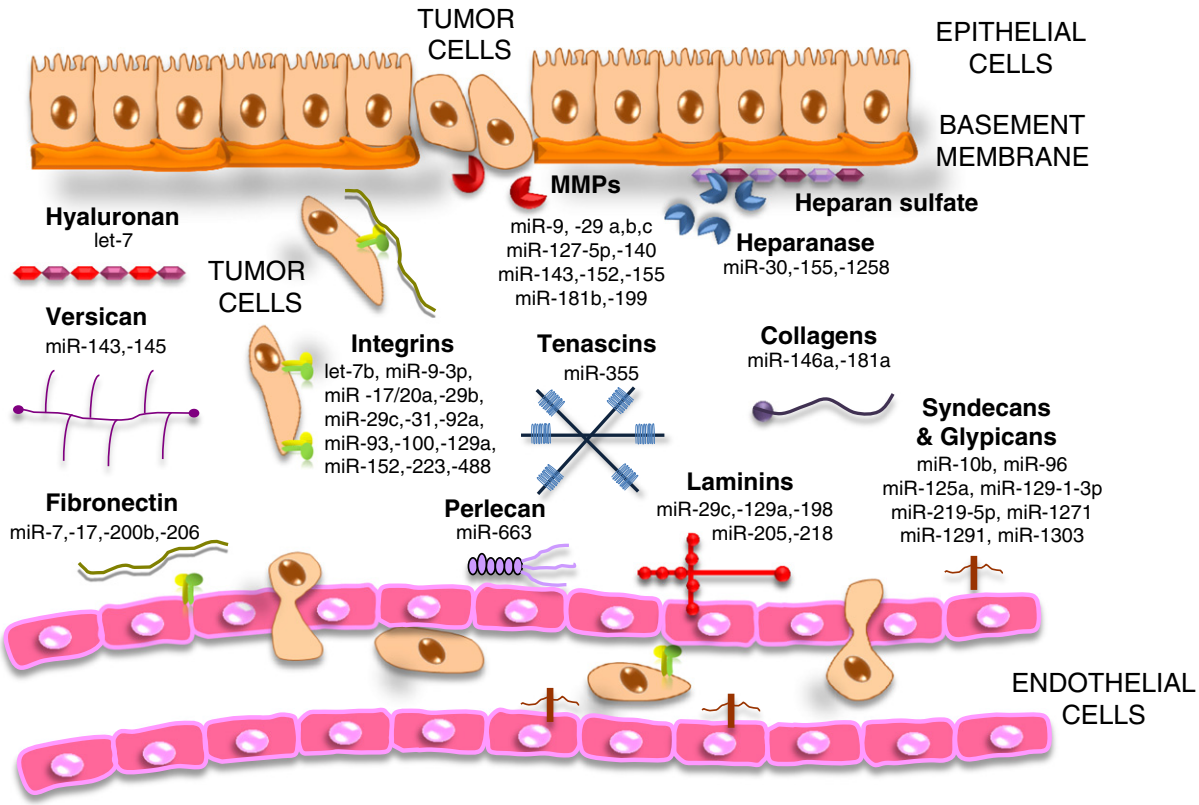

Fig. 2. Selected ECM constituents and their receptors as miRNA targets in tumor metastasis. The interstitial matrix and basement membranes of epithelia and endothelia are composed of a network of large glycoproteins (collagens, laminins, fibronectin, tenascins), proteoglycans (perlecan, versican) and glycosaminoglycans (hyaluronan). Via cell surface receptors and coreceptors of the integrin, syndecan and glypican families, cells can interact with the ECM, resulting in changes in cell behavior. The ECM can be remodeled by enzymes such as MMPs or heparanase. miRNAs are capable of regulating the expression of these genes at the posttranscriptional level for each specific subclass of molecules (see text for details on family member/chain-specific miRNAs). During tumor progression and metastasis, epithelium-derived cancer cells must initially loosen cell–cell and cell–matrix contact and acquire a migratory phenotype via the process of EMT. The initial steps of metastasis are guided by increased activity of MMPs and heparanase, leading to the removal of mechanicophysical hindrances and to the release of growth factors from the matrix. Alterations in the expression and interaction of integrins and their matrix substrates promote invasiveness. Tumor cells finally enter the circulation, supported by the process of tumor angiogenesis, and exit the blood vessels at distant metastatic sites. Heparanase and MMP-mediated degradation of endothelial basement membranes, integrin- and syndecan-modulated changes in tumor cell–endothelial interactions, and heparan sulfate-stimulated chemokine activity play major roles in this process [69,82].

the target mRNA [16,17]. However, in many cases, indirect effects, such as targeting of transcriptional repressors or activators by a specific miRNA, have to be considered. Such a mode of regulation has been described for a number of ECM components, ECM-remodeling MMPs and ECM receptors. For example, targeting of the transcription factor Ets-1 by miR-199a-5p reduced MMP-1 induction during wound repair, leading to decreased angiogenesis, wound closure, and insufficient granulation tissue formation [47]. Moreover, miR-9 overexpression retarded uveal melanoma cell migration and invasion via direct targeting of nuclear factor-κB (NF-κB)-mediated downregulation of MMP-2, MMP-9 and VEGF-A [48]. Apart from matrix remodeling factors, individual chains of large basement membrane glycoproteins of the laminin family are regulated in an indirect manner by miRNAs. For example, let-7-induced downregulation of the transcriptional regulator HMGA2 hampered mRNA translation of the glomerular basement membrane component laminin-β2 [49]. Furthermore, miR-205 hinders prostate cancer progression by regulating the deposition of laminin-332 and expression of its receptor integrin-β4 by targeting the transcriptional modulator ΔNp63α – involved in the maintenance of the basement membrane – through proteasomal degradation [49]. In the case of the cell surface proteoglycan glypican-3, a different mechanism of indirect miRNA regulation was reported for hepatoma cells: miR-1291 was shown to repress mRNA expression of the ER stress sensor IRE1α via interaction with 5′ UTR. IRE1α in turn cleaved glypican-3 mRNA at a 3′ UTR consensus site, resulting in glypican-3 mRNA degradation [51]. Thus, miR-1291 exerted its regulatory effect by silencing a negative regulator of glypican-3 in the absence of any direct interaction between miR-1291 and glypican-3 mRNA.

2.3. Epigenetic regulation of ECM-targeting miRNAs

As miRNAs are chromosomally encoded, their genes can be subject to epigenetic regulation, affecting their own expression, and consequently expression of their target genes. For example, a recent study on chemotherapy-resistant MDA-MB-231 breast cancer cell subclones revealed that the miR-663 gene was hypomethylated compared to the parental cell line. The resulting miR-663 upregulation was associated with a downregulation of the large matrix proteoglycan perlecan (HSPG2), leading the authors to suggest a link between altered matrix biosynthesis and resistance to chemotherapy [52]. In hepatocellular carcinoma tissues and cell lines, miR-125b expression was shown to be epigenetically silenced, potentiating the invasive phenotype [53]. Restoration of miR-125b expression suppressed hepatocellular carcinoma cell proliferation, anchorage-independent growth, and migration through direct targeting of placental growth factor along with a dysregulation of MMP-2 and MMP-9 expression. Therefore, altered matrix remodeling and liberation of growth factors may have accounted for the observed inhibition of cellular invasion and angiogenesis. A different link to epigenetic regulation was revealed by Chen et al. [54]: Treatment of primary human aortic smooth muscle cells with oxidized low-density

Table 1
MicroRNA regulation of matrix-dependent cellular processes. ECM-mediated signals affect miRNA expression, while in turn miRNA regulation of ECM composition affects various cellular processes. Selected examples are shown focussing largely on direct regulatory interactions. See main text for details.

ECM-related molecule	miRNA regulating ECM	miRNA regulated by ECM	Biological processes affected	References
Proteoglycans and glycosaminoglycans				
Hyaluronan/CD44		miR-21, miR-302	Invasiveness, apoptosis, chemotherapy resistance, stem cell properties	[8,9,65,66]
Aggrecan	miR-1, miR-181a		Chondrogenic differentiation	[111,112]
Decorin		miR-21	Inflammation	[124]
Glypican-3	miR-96, miR-1271, miR-219-5p, miR-520c-3p, miR-129-1-3p (upregulation), miR-1291 (upregulation), miR-1303 (upregulation)		Apoptosis and growth inhibition, cell cycle arrest	[27,74–76]
Glypican-4	miR-125a		Growth inhibition	[77]
Perlecan	miR-663		Chemotherapy resistance	[52]
Syndecan-1	miR-10b		Cell motility, invasiveness, resistance to radiotherapy, IL-6 secretion, signaling (FAK/β-integrin/HGF)	[32,125]
Versican	miR-143, miR-199a* (upregulation)	miR-133a, miR-199a*, miR-144, miR-431	Organ adhesion, tumor growth, proliferation, survival, migration, invasion, colony formation, growth factor stimulates cell migration	[59–61,92]
Matrix glycoproteins				
Collagen XVI	miR-181a		Fibroblast senescence	[73]
Fibronectin	miR-7, miR-17, miR-200b, miR-206		Survival, proliferation, migration, EMT	[70,71,113,115]
LAMC1	miR-124a, miR-205		Cell proliferation, cell cycle progression, clonogenic potential, impaired tumor growth, cell migration and invasion	[72,95]
LAMC2	miR-29a/b/c		Cell migration and invasion	[94]
SPARC	miR-29a		Cell invasion	[99]
Tenascin C	miR-335		Cell migration	[90]
Matrix receptors				
CD44	miR-199a-3p, miR-328	miR-216a, miR-328, miR-330, miR-491, miR-512-3p, miR-608, miR-671	Cell proliferation, survival, metastasis, cell adhesion, chemotherapy resistance	[62,63,85,100]
Integrin alpha6beta4		miR-29a	Cell invasion	[99]
Integrin alphavbeta3	miR-100		Angiogenesis	[120]
ITGA2	miR-31		Cell spreading, metastasis	[96]
ITGA5	miR-31, miR-92a, miR-152		Fibroblast senescence, adhesion to collagen I, cell spreading, angiogenesis, metastasis	[73,96,121]
ITGA6	miR-29a/b/c		Cell migration and invasion	[94]
ITGAV	miR-31		Cell spreading, metastasis	[96]
ITGB1	miR-9-3p, miR-124, miR-183		Cell adhesion, migration, invasion	[83,84,95,134]
ITGB4		miR-92ab, miR-99ab/100	Metastasis	[67]
ITGB5		miR-125b	Anoikis resistance of mesenchymal stem cells	[68]
ITGB8	miR-93		Angiogenesis, tumor growth	[119]
Biosynthetic enzymes				
NDST1 (heparan sulfate)	miR-24		Angiogenesis (VEGF-A)	[35]
HAS2 (hyaluronan)	Let-7		Survival, cell adhesion, invasiveness	[37]
ECM-degrading enzymes/inhibitors				
Sulf1	miR-21, miR-516a-3p		Survival, cell proliferation, tumor growth, Wnt-dependent metastasis	[41,42]
Heparanase	miR-1258		Invasiveness, metastasis	[45,46
MMP-2	miR-29b, miR-125b, miR-488		Invasiveness, cell migration, angiogenesis, chondrogenic differentiation	[53,54,110,122]
MMP-9	miR-29b, miR-125b, miR-181a (upregulation)		Invasiveness, cell migration	[53,56,102]
MMP-13	miR-9, miR-127-5p, miR-140, miR-143		Cell migration and invasion, inflammation	[103,126–128]
MMP-16	miR-155		Cardiomyocyte progenitor cell migration	[101]
Neuroserpin	miR-21		Inhibition of cell cycle arrest	[78]
PAI-I	miR-145		Invasiveness	[104]
TIMP-3	miR-181a		invasiveness	[102]

lipoprotein (LDL) downregulated DNA methyltransferase 3b via upregulation of miR-29b expression in a dose-dependent manner. In turn, reduction of DNA methyltransferase 3b expression leads to enhanced cell migration through epigenetic upregulation of the MMP-2 and MMP-9 genes.

2.4. Coregulation of miRNAs with ECM receptors

In some instances, the gene encoding a specific miRNA can be contained within an intron of a protein-coding gene. This is the case for murine miR-717, which resides in the intron 3 of the cell surface HS proteoglycan glypican-3 [55]. While the direct functional significance of this finding has not been established, yet, it is important to consider a potential coregulation of the primary glypican-3 transcript and miR-717. For example, the effects of glypican-3 gene deletions encompassing the miR-717-encoding intron may cause miR-717-dependent indirect effects in mice. One could speculate if the partial phenocopy of the Simpson–Golabi–Behmel syndrome of glypican-3-deficient mice [56] could have been modified in a miR-717-dependent manner. Moreover, (patho)physiological contexts promoting up- or downregulation of murine glypican-3 transcription should also affect miR-717, and expression of its targets. Clearly, more research is needed

to assess the full impact of a coregulation of intron-encoded miRNAs with the primary transcripts of their host genes.

2.5. Regulation of miRNA activity via the 3′UTR of ECM mRNAs

The most common mode of miRNA-mediated target regulation involves interactions between the miRNA 'seed'-sequence and the 3′UTR of the target mRNA (Fig. 1). Interestingly, the 3′UTRs of some mRNAs can negatively regulate miRNAs, thus acting as so-called competing endogenous RNAs (ceRNAs) [57]. A prominent example for this mode of regulation is the 3′UTR of the large chondroitin sulfate proteoglycan versican, a multifunctional interaction partner for a variety of ECM-related molecules, including hyaluronan, tenascin, and matrix receptors such as CD44 and integrins [58].

As a ceRNA, versican induced organ adhesion in transgenic mice expressing its 3′UTR by regulating the function of miR-199a* [59]. Expression of the predicted miR-199a*-targets versican and fibronectin was upregulated in these mice, suggesting that their mRNAs were freed from being repressed by this miRNA via competitive binding to versican 3′UTR. In an extension of this work, it was shown that the 3′UTR of versican could modulate the function of additional miRNAs, leading to an upregulation of miRNA-controlled tumor suppressor genes und a reduction of breast cancer cell growth in a mouse model [60]. Moreover, upregulation of the versican 3′UTR in hepatocellular carcinoma cells increased proliferation, survival, migration, invasion, and colony formation, which could be linked to functional interactions with miRNAs miR-133a, miR-199a*, miR-144, and miR-431 [61]. Along with increased CD34 expression, the resulting upregulation of versican and the interstitial matrix glycoprotein fibronectin were identified as contributing factors to the tumor-promoting functions of versican ceRNA. Apart from versican, a ceRNA activity has been assigned to the 3′UTR of CD44, a cell surface glycoprotein interacting with several ECM molecules, including hyaluronan, collagens, and versican. Via regulation of miR-216a, miR-328, miR-330, miR-491, miR-512-3p, miR-608 and miR-671, the 3′UTR of CD44 increased the expression of CD44, CDC42, a small GTPase implicated in modulating cell motility, and the interstitial matrix glycoproteins fibronectin and collagen I (alpha 1 chain) [62,63]. As a consequence of matrix remodeling, cell proliferation and survival were decreased in the human breast cancer cell line MT-1, whereas metastasis of MDA-MB-231 breast cancer cells was promoted.

2.6. Matrix-mediated signaling processes regulating miRNA expression

It is now well established that the ECM does not only have a structural role, but that it can also induce and modulate signaling processes via interactions of matrix glycoproteins and glycans with cell surface matrix receptors such as integrins, CD44 and cell surface proteoglycans [4,5,40,64]. These ECM-mediated signaling events have been shown to influence miRNA expression, which in turn induces changes in cellular phenotype. For example, interaction of the matrix glycosaminoglycan hyaluronan with its receptor CD44 promoted association with protein kinase C in MCF-7 breast cancer cells [9]. Activation of this signaling pathway leads to an activation of the pluripotency-associated transcription factor Nanog, which became associated with the RNase III Drosha and the RNA helicase p68, resulting in upregulation of miR-21. The following upregulation of inhibitors of apoptosis proteins and the multidrug-resistance protein MDR1 induced anti-apoptosis and chemotherapy resistance. Similar findings were made in head and neck squamous cell carcinoma cells, involving a slightly different mechanism which included Nanog–STAT3-interactions, and upregulation of miR-302 [65,66]. Besides hyaluronan–CD44 interactions, interactions of integrins with their matrix substrates have been shown to induce altered miRNA expression. Integrin α6β4, an adhesion receptor for laminins, major compounds of basement membranes, plays an essential role in cancer cell motility. Mechanistically, miR-92ab and miR-99ab/100 family members were dysregulated upon β4-integrin-silencing in breast cancer cell lines, suggesting an impact of integrin signaling on prometastatic miRNA expression [67]. Likewise, miR-125b expression was upregulated upon integrin β5 silencing, leading to the induction of anoikis resistance in mesenchymal stem cells [68].

3. Specific ECM-dependent cellular processes regulated by miRNAs

The ECM does not only provide mechanical support for cells, the complex amalgam of collagens, large glycoproteins, proteoglycans and glycosaminoglycans, but also serves as a reservoir of cytokines, chemokines and morphogens, and provides specific binding sites for cell surface receptors and coreceptors such as integrins, cell surface proteoglycans and hyaluronan receptors. Thereby, the ECM is capable of inducing intracellular signaling events, which in turn modulate cell behavior. In the following section, we will have a closer look at how miRNAs regulate specific cellular processes by modulating the expression of ECM compounds, of their receptors, and of enzymes modifying their functional properties.

3.1. Cell proliferation, survival and apoptosis

The classical concept of anchorage-dependent growth has taught cell biologists early on that interactions of cells with their ECM are an important requirement for cell survival and proliferation. Specific interactions between large matrix glycoproteins such as fibronectin and laminins and their integrin counterreceptors [5,6] trigger signaling cascades which ensure cell survival, while the absence of such signals leads to induction of apoptosis. Likewise, growth factors stored in the ECM via binding to proteoglycans and glycosaminoglycans interact with their cognate receptor tyrosine kinases or serine/threonine kinases to initiate signaling processes augmented by cell surface HS proteoglycans, thus promoting cell proliferation [64,69], or, in the case of the cytokine tumor necrosis factor (TNF)-α, apoptosis. Several publications have demonstrated a link between proliferation and miRNA-induced regulation of fibronectin. In bronchopulmonary dysplasia disorder, enhanced cell survival, proliferation and migration are mediated by increased fibronectin production, which could be suppressed by overexpression of miR-206 directly targeting fibronectin mRNA [70]. Moreover, miR-17 overexpression in transgenic mice suppressed the expression of fibronectin and fibronectin type-III domain containing 3A, thus reducing cell proliferation and migration in vitro and growth retardation in vivo [71]. In addition to fibronectin, miRNA induced targeting of laminin can affect cell proliferation: For example, restored miR-205 expression reduced cell proliferation, cell cycle progression and clonogenic potential in vitro, and impaired tumor growth in vivo, via targeting LAMC1 [72]. Concerning the role of matrix receptors, we already learned about the impact of CD44–hyaluronan interactions and of integrin β5 on miRNA-dependent regulation of cell proliferation and (anti-) apoptosis in Section 3.1. Human dermal fibroblast senescence could be induced by miR-152 and miR-181a mediated-downregulation of integrin α5 and collagen XVI expression, resulting in reduced cellular adhesion and extracellular remodeling [73]. Among cell surface HS proteoglycans, miR-10b-dependent regulation of syndecan-1 was shown to affect matrix-dependent cell proliferation, whereas, several publications identified miRNA targeting of glypican family members as a mode for the regulation of cell proliferation and survival: Screening a library of 876 individual miRNAs and glypican-3 mRNA in hepatocellular carcinoma samples, Maurel et al. [74] identified 5 miRNAs capable of modulating glypican-3 expression. Whereas miR-96 and its paralog miR-1271 repressed expression, miR-129-1-3p, miR-1291, and miR-1303 had an inducible effect. Functional analysis revealed that miR-1271 inhibited the growth of hepatocellular carcinoma cells in a glypican-3-dependent manner and induced cell death. Similar findings were independently reported for miR-219-5p, which inhibited hepatocellular carcinoma cell proliferation in vitro, and caused cell cycle arrest at the G1 to S transition [75], and for miR-520c-3p, which inhibited cell

proliferation and invasion by inducing apoptosis via targeting glypican-3 [76]. Targeting of glypican-4 by miR-125a was reported to inhibit growth of human HEK293T kidney cells through a mechanism involving growth-factor-dependent activation of the MAPK pathway [77], in accordance with the role of HS proteoglycans as coreceptors for growth factor-mediated receptor tyrosine kinase signaling [64,69]. Finally, miRNA-dependent regulation of protease inhibitors implicated in matrix remodeling has been described as a mechanism for regulating cell proliferation. For example, targeting of serpini1/neuroserpin, an inhibitor of tissue plasminogen activator by miR-21 inhibits G1/S cell cycle arrest, thus potentiating gastric cancer growth [78].

3.2. Cell adhesion

Cell adhesion plays a pivotal role during development, where specific matrix substrates provide migratory tracks e.g. for directional growth of axons and non-neural cell populations [79]. The deleterious effect of aberrant matrix function in development is illustrated by the often severe phenotypes of knockout mice lacking specific ECM or ECM receptor genes, such as mice lacking fibronectin or β-integrins [80,81]. However, cell adhesion also plays an important role in a pathophysiological context, e.g. during cancer metastasis: At early stages, cancer cells need to loosen cell–cell and cell–matrix contact in order to acquire a migratory phenotype, while at later stages cancer cells need to regain adhesiveness in order to leave the circulation and to establish secondary tumors at sites of distant metastasis [82] (Fig. 2). In this respect, cell adhesion is closely linked to cell migration, which will be discussed in Section 3.3. The integrin family of matrix receptors is a natural target for miRNAs with respect to the modulation of cell adhesion to the ECM. Indeed, miRNA-mediated downregulation of integrin subunits has been shown to result in altered cell adhesion in several cases. Overexpression of miR-152 in human dermal fibroblasts resulted in 3′UTR-mediated downregulation of integrin α5 and reduced adhesion to type I collagen [73]. Moreover, overexpression of miR-183 reduced adhesion to laminin, gelatin, and collagen type I in normal human fibroblasts and human trabecular meshwork cells via targeting of integrin β1, suggesting its involvement in regulating metastasis and cell senescence [83]. Similarly, miR-124 impaired oral squamous cell carcinoma cell adhesion via downregulation of β1-integrin through interacting with its 3′UTR [84]. Besides integrin-mediated adhesion, miRNA interference with hyaluronan or its receptor CD44 modulates cell adhesion. For example, miR-328 diminished A431 cell adhesion to hyaluronan and fibronectin, but not to laminin, via repression of its direct target CD44 [85]. In contrast, adhesion of breast and cervical carcinoma cells was promoted by inhibition of let-7, which resulted in upregulation of hyaluronan synthase 2 [35].

3.3. Cell motility

Like cell adhesion, cell migration is of major importance for embryonic development, wound repair, and pathological processes such as cancer metastasis. Matrix-dependent signaling processes trigger a restructuring of the cellular cytoskeleton, which results in a change of cell motility [86–88]. In addition, cytokine-induced reprogramming processes can result in acquisition of a migratory phenotype, as exemplified by the process of epithelial-to-mesenchymal transition (EMT) [89]. Several studies have reported changes in cell motility due to miRNA-dependent alteration of matrix substrate expression. miR-335, a breast cancer metastasis suppressor, repressed cell migration via targeting the progenitor cell transcription factor SOX4 and the ECM glycoprotein tenascin-C [90]. Restoration of mir-335 expression also inhibited hepatic stellate cell migration and activation via tenascin-C downregulation, associated with reduced α-smooth muscle actin and collagen type I expression [91]. The large extracellular chondroitin sulfate proteoglycan versican is produced by smooth muscle cells (SMCs) and promotes their migration and proliferation [58,92]. Notably, the transcriptional coactivator myocardin can regulate versican expression via induction of miR-143, which targets the 3′UTR of versican, leading to its downregulation. This mode of regulation has an impact on platelet-derived growth factor BB-induced SMC migration [92]. Apart from versican, numerous publications report miRNA-mediated regulation of laminin expression as a contributing factor to changes in cell motility. The laminin family of large extracellular glycoprotein plays a major role in establishing the complex network of basement-membrane-like extracellular matrices. Composed of three chains, the cross-shaped laminins provide binding sites for integrins, heparan sulfate proteoglycans, and multiple adaptor-like proteins via their multidomain structure [93]. Functional interactions with integrins thereby induce signaling processes which alter cell behavior. Interestingly, some microRNAs coregulate laminin and integrin subunits, underscoring the importance of these matrix receptors for miRNA-dependent regulation of cell motility. For example, re-expression of multiple miR-29 family members (miR-29a/b/c) impaired the migratory and invasive phenotype of head and neck squamous cell carcinoma cell lines via direct targeting of LAMC2 and α6 integrin [94]. Furthermore, miR-124a downregulation is a frequent event in glioblastoma associated negatively with the expression of target proteins, such as LAMC1 and integrin β1, thus hindering migration and invasion of glioblastoma cells [95]. Numerous additional examples for miRNA-mediated regulation of integrin subunits have been described: It has been reported that miR-31, a master regulator of integrins, directly targets multiple α subunit partners (α2, α5, and αV) of β1 integrins and also β3 integrins. Overexpression of miR-31 in cancer cells significantly inhibited cell spreading in a ligand-dependent manner and thereby modulated key functions of cancer cell invasion and metastasis [96]. miR-31 overexpression also antagonizes breast cancer metastasis in vivo including local invasion, early post-intravasation events, and metastatic colonization via suppression of a panel of the pro-metastatic target genes integrin alpha5, radixin, and RhoA [97]. While these examples show the relevance of miRNA-regulation of integrin expression for cell motility in physiological and pathophysiological contexts, it is clear that the miRNAs are usually targeting additional mRNAs, resulting in an enhanced, or at least a more complex combinatorial effect on the target cell(s). Finally, differential regulation of integrin expression can result in altered miRNA expression affecting ECM biosynthesis. Secreted protein acidic and rich in cysteine (SPARC) is a glycoprotein playing an important role in matrix remodeling and invasion [98]. Overexpression and activation of the laminin receptor α6β4 integrin in breast carcinoma cells resulted in augmented SPARC expression via downregulation of the SPARC-targeting miRNA miR-29a, thus facilitating cellular invasion [99]. Apart from the interaction of integrins with their fibronectin and laminin matrix substrates, miRNA-modulation of the interaction of hyaluronan and its receptor CD44 affects cell migration. Importantly, enhanced hyaluronan-dependent invasiveness and chemotherapy resistance of CD44+ hepatocellular carcinoma cells could be inhibited upon direct targeting of CD44 via miR-199a-3p overexpression [100].

Within their extracellular environment, cell motility is not solely determined by matrix–receptor interactions and the resulting signaling processes that lead to cytoskeletal restructuring, but also by degradation of the ECM, which removes physical hindrances of migratory processes. Therefore, miRNA-dependent regulation of matrix-degrading enzymes and their inhibitors additionally influences cell motility within tissues. By directly targeting MMP-16, miR-155 significantly inhibited cell migration in human cardiomyocyte progenitor cells [101]. Overexpression of miR-181a enhanced invasion of human MG63 osteosarcoma cells, which was associated with upregulation of MMP-9 and the downregulation of TIMP-3 [102]. Furthermore, inhibition of prostate cancer cell migration and invasion were shown to be mediated by miR-143-induced MMP-13 downregulation [103]. Finally, plasminogen activator inhibitor PAI-1 was down-regulated at the mRNA and protein levels upon miR-145 transfection in a human endometriotic cell line, which

was associated with reduced invasion [104]. Several additional examples for miRNA-dependent remodeling of ECM, and the associated changes in cell motility, have been recently reviewed by Rutnam et al. [20].

3.4. Stem cell function and cell differentiation

In contrast to differentiated cells, which fulfill a specific function within a given tissue, stem cells are characterized by the property of self-renewal and asymmetric cell division, giving rise to a daughter cell with stem cell properties, and a committed daughter cell capable of undergoing further differentiation processes [104,105]. Regarding pathophysiological processes, a subpopulation of cancer cells is characterized by stem cell-like properties, including self-renewal, unlimited and high proliferative potential, expression of multidrug-resistance proteins, active DNA repair capacity, apoptosis resistance, and a high developmental plasticity [105,106]. These apparent similarities have lead to the concept of cancer stem cells, which proposes that undifferentiated stem-like cells within the tumor may be the source of the highly proliferative bulk tumor cells. As summarized in several contributions to this special issue, the ECM has a profound influence on the maintenance of the undifferentiated state of stem cells, and on driving cells into defined lineages of differentiation [107–109]. Therefore, it is not surprising that miRNA-dependent regulation of ECM constituents has an impact on (cancer) stem cell function and differentiation processes. For example, miR-125b expression was shown to be upregulated by integrin β5 silencing and to induce anoikis resistance in mesenchymal stem cells [68]. In addition, the interaction of hyaluronan and a CD44 variant has an impact on a cancer stem cell phenotype: In head and neck squamous cell carcinoma, interaction of hyaluronan with CD44v3 leads to complex formation with the pluripotency-associated transcription factors Oct4, Sox2 and Nanog, which are controlling expression of miR-302 at the promoter level [66]. Upregulated miR-302, miRNA-dependent targeting of DNA demethylation regulators, and upregulation of survival proteins enhanced cancer stem cell properties, including self-renewal, clonogenicity, and chemotherapy resistance in hyaluronan–CD44v3-activated head and neck cancer.

Concerning the modulation of differentiation processes, numerous examples of miRNA-mediated ECM modulation have been described. Interference with miR-488 function induced upregulation of MMP-2, thus preventing cellular condensation and chondrogenic differentiation [110]. Moreover, using microarray analysis, Sumiyoshi et al. [111] found that the expression of miR-1 was most repressed upon hypertrophic differentiation. In vitro transfection studies of chondrocytes revealed that aggrecan, the major cartilaginous proteoglycan, was a target of miR-1, which emerged as an important regulator of the chondrocytic phenotype [111]. An independent study revealed that miR-181a repressed the expression of aggrecan, and the chondrogenesis-promoting factor CCN1 [112]. A more indirect impact on cartilage differentiation has been reported by Gradus et al. [113]. They could demonstrate that expression of Snail1, a fibroblast growth factor (FGF) effector responsible for derailing the normal program of permanent chondrocytes, is controlled by miR-125b and miR-30a/c. The authors found that inhibition of these miRNAs in chondrocytes resulted in a derepression of Snail1 and consequently in reduced expression of aggrecan and collagen 2 (alpha 1). Additional aspects of miRNA-regulated cartilage differentiation have been recently reviewed by Rutnam et al. [20]. Apart from cartilage differentiation, the process of EMT is modulated via miRNA regulation of ECM constituents. For example, miR-200b mediated inhibition of TGF-β1-induced EMT via direct repression of fibronectin synthesis in renal fibrosis [114]. In contrast, downregulation of miR-7 in breast cancer cells induced EMT by enhancing the expression of vimentin and fibronectin and repression of the epithelial cell adhesion molecule E-cadherin [115].

4. Pathophysiological, diagnostic and therapeutic relevance of miRNA-dependent ECM regulation

The expression of miRNAs is dysregulated under a variety of pathological conditions, suggesting a microRNA involvement in the pathogenetic process [3,116]. In the preceding chapters, we have encountered several examples for miRNA-dependent regulation of ECM constituents as modulators of important pathogenetic properties of cancer cells, including aberrant proliferation, apoptosis resistance, cell migration and metastasis, and cancer stem cell properties. Another hallmark of cancer is tumor angiogenesis, the formation of blood vessels from existing vasculature, which is initiated and sustained by secretion of angiogenic cytokines by tumor cells to ensure a sufficient nutrient supply [69]. The ECM and its receptors are known to be important regulators of physiological and pathological angiogenesis [64,117,118]. Several publications identified miRNA-dependent regulation of integrin subunits as an angiogenesis-modulating mechanism. miR-93 was shown to augment angiogenesis and tumor growth in human glioblastoma via targeting integrin-β8 [119]. In intestinal acute graft-versus-host disease in mouse models and patients, a protective role for miR-100 in blocking inflammatory neovascularization was attributed to its targeting of αvβ3 integrin expression [120]. Moreover, miR-92a curtailed angiogenesis and functional recovery of ischemic tissues via targeting of the proangiogenic integrin subunit α5 [121]. Apart from integrins, MMPs are involved in regulating angiogenesis. For example, miR-29 overexpressing hepatocellular carcinoma cells exhibit reduced tumor angiogenesis, invasion, and metastasis through direct targeting of the 3′-UTR of MMP-2 mRNA [122]. Moreover, miR-24 suppression of NDST1 reduced endothelial cell responsiveness to one of the most important proangiogenic cytokines, VEGF-A [35], in accordance with the role of cell surface HS proteoglycans as coreceptors for receptor tyrosine kinases [69].

miRNA-dependent regulation of ECM constituents also plays a role in the pathogenesis of various inflammatory diseases. The interstitial dermatan sulfate proteoglycan decorin has recently emerged as a novel regulator of allergic inflammation [123]. Merline et al. [124] demonstrated that decorin-mediated activation of toll-like receptors was mechanistically linked to a decreased expression of miR-21, which in turn prevented the repression of the proinflammatory factor PDCD4 [124], thus marking soluble decorin as a proinflammatory factor in sepsis. In endometriosis, an inflammatory disease associated with ectopic growth of endometrial tissue, miR-10b-dependent targeting of the HS proteoglycan syndecan-1 was shown to modulate interleukin (IL)-6 expression and hepatocyte growth factor induced MAPK signaling [125]. In human osteoarthritis, miR-9 overexpression inhibits the secretion of the collagen type II-targeting metalloproteinase MMP-13 and IL-1β-induced TNF-alpha production [126]. Moreover, miR-127-5p and miR-140 abrogated IL-1β-induced MMP-13 production in chondrogenic SW1353 cells and human articular chondrocyte C28/I2 cells respectively, as measured by a MMP-13 3′UTR reporter construct, suggesting its potential role in the development of osteoarthritis [127,128].

The mechanistic involvement of dysregulated miRNA function in disease raises the question of a potential use of miRNAs as diagnostic markers or therapeutic targets. In fact, due to their comparable high stability in patient tissue samples and sera, and due to highly sensitive qPCR-based detection techniques, miRNAs are promising diagnostic markers from a technical perspective. As diagnostically relevant alterations in miRNA expression are not specific for ECM-related genes, the reader is referred to reviews by Götte [3] and Neubauer et al. [116] in this context. However, with respect to ECM-specific miRNA-related diagnostics, the investigation of single nucleotide polymorphisms (SNPs) is of relevance. For example, a clinical association has found between the risk of prostate cancer and the SNP rs11902171 in the predicted miRNA-binding site of the ITGAV integrin gene [129]. Furthermore, the A allele of the SNP rs743554 in the predicted miRNA target

site of the ITGB4 integrin gene has been reported to be strongly associated with estrogen receptor-negative tumors and survival in a study on 749 Swedish breast cancer patients, marking it as a potential prognostic factor in breast cancer [130]. While this is clearly just a beginning, it can be expected that the discovery of additional SNPs in miRNA binding sites of selected ECM-related molecules may expand the repertoire of diagnostic, prognostic, or predictive disease markers in the near future.

The high regulatory capacity of miRNAs, and their mechanistic involvement in pathologies, marks them as potential therapeutic targets, or as potential therapeutics, respectively, depending on if up- or downregulation of a particular miRNA is linked to the disease. In the case of an upregulation, miRNA can be antagonized using 2′-O-methyl RNA oligonucleotides, locked nucleic acid-antimiRs (antisense miRNA), cholesterol-conjugated antagomiRs, or miRNA decoys, which are synthetic mRNAs expressing complementary target sequences, thus competing with the endogenous target mRNAs of a miRNA. To induce upregulation of a miRNA, transfection with miRNA mimics represents an approach which has been proven successful in vitro and in animal models (see [3,116] for discussion). For example, lentiviral miR-30-based RNA interference against heparanase abrogated melanoma metastasis in a xenograft animal model [131]. Although most therapeutic effects reported so far have been achieved using preclinical in vitro and animal models, some of these results are highly encouraging. Prime examples are the LNA-antimiR-treatment of miR-122-associated hypercholesterinemia, which resulted in low plasma cholesterol levels due to upregulation of cholesterol synthesis inhibiting factors in a non-human primate model [132], or preclinical trials involving a LNA-based miRNA-targeting drug against liver-specific miR-122 for the treatment of hepatitis C, as miR-122 stimulates hepatitis C virus replication [133]. In some cases, modified ECM compounds have been successfully utilized as delivery vehicles for miRNA drugs. For example, atelocollagen-mediated delivery of a miR-516a-3p expression vector into orthotopic human scirrhous gastric carcinoma cells prolonged the survival in a mouse model, due to Sulf-1 downregulation [42]. Moreover, interference with ECM-targeting miRNA function can result in beneficial effects when combined with conventional therapies. For example, downregulation of the perlecan-targeting miRNA miR-663 is associated with increased chemotherapy sensitivity of breast cancer cells [52]. Likewise, interference with miRNAs regulating the hyaluronan–CD44 signaling axis, such as miR-21 or miR-199a-3p, influences chemotherapy resistance [65,100]. Furthermore, a synergistic growth-inhibiting effect between the β1-integrin targeting miR-9-3p and the MEK1/2 inhibitor AZD6244 on human breast cancer cells has been described [134].

The near future will reveal if ECM-modulating miRNA-centered therapeutic approaches can be successfully transferred into clinical settings. Apart from classical obstacles associated with targeted delivery, which need to be overcome [135], the potential danger of causing side effects due to the multitude of predicted targets of a particular miRNA is an issue that needs to be carefully addressed. On the other hand, synchronous targeting of multiple mRNAs by a particular miRNA-drug may result in a much stronger therapeutic effect compared to a single molecule approach (see [3,116,135] for discussion).

5. Conclusion and perspectives

miRNAs have emerged as important and powerful posttranscriptional regulators of numerous cellular processes [2,3,116]. Among their targets, ECM-constituents and their receptors have been identified as important modulators of cell behavior, having an impact on cell proliferation, survival and apoptosis, cell differentiation and stemness, cell adhesion and migration. Coregulation with ECM mRNAs, ceRNA functions of the 3′UTRs of ECM-related mRNAs, and matrix-mediated signaling controlling the expression of miRNAs are molecular mechanisms by which complex regulatory circuits between miRNA and ECM gene expression are controlled. As dysregulated expression of ECM-targeting miRNAs has been linked to the pathogenesis of a variety of disorders, including inflammatory and malignant diseases, these miRNAs emerge as diagnostic and prognostic markers and as therapeutic targets. While encouraging results have been achieved in vitro and in animal models, more research is needed to fully establish the therapeutic and diagnostic value of ECM-related miRNAs. Apart from the technical challenge of a targeted delivery of miRNA-related drugs, the issue of potential side effects associated with the multitude of potential target sequences will require particular attention.

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References

[1] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2004) 281–297.
[2] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell 136 (2009) 215–233.
[3] M. Götte, MicroRNAs in breast cancer pathogenesis, Minerva Ginecol. 62 (2010) 559–654.
[4] A. Genasetti, D. Vigetti, M. Viola, E. Karousou, P. Moretto, M. Rizzi, B. Bartolini, M. Clerici, F. Pallotti, G. De Luca, A. Passi, Hyaluronan and human endothelial cell behavior, Connect Tissue Res 49 (2008) 120–123.
[5] S.H. Kim, J. Turnbull, S. Guimond, Extracellular matrix and cell signalling: the dynamic cooperation of integrin, proteoglycan and growth factor receptor, J. Endocrinol. 209 (2011) 139–151.
[6] A. Domogatskaya, S. Rodin, K. Tryggvason, Functional diversity of laminins, Annu. Rev. Cell Dev. Biol. 28 (2012) 523–553.
[7] K.J. Price, A. Tsykin, K.M. Giles, R.T. Sladic, M.R. Epis, R. Ganss, G.J. Goodall, P.J. Leedman, Matrigel basement membrane matrix influences expression of microRNAs in cancer cell lines, Biochem. Biophys. Res. Commun. 427 (2012) 343–348.
[8] H.J. Kwak, Y.J. Kim, K.R. Chun, Y.M. Woo, S.J. Park, J.A. Jeong, S.H. Jo, T.H. Kim, H.S. Min, J.S. Chae, E.J. Choi, G. Kim, S.H. Shin, H.S. Gwak, S.K. Kim, E.K. Hong, G.K. Lee, K.H. Choi, J.H. Kim, H. Yoo, J.B. Park, S.H. Lee, Downregulation of Spry2 by miR-21 triggers malignancy in human gliomas, Oncogene 30 (2011) 2433–2442.
[9] L.Y. Bourguignon, C.C. Spevak, G. Wong, W. Xia, E. Gilad, Hyaluronan–CD44 interaction with protein kinase C(epsilon) promotes oncogenic signaling by the stem cell marker Nanog and the production of microRNA-21, leading to down-regulation of the tumor suppressor protein PDCD4, anti-apoptosis, and chemotherapy resistance in breast tumor cells, J. Biol. Chem. 284 (2009) 26533–26546.
[10] R.C. Lee, R.L. Feinbaum, V. Ambros, The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14, Cell 75 (1993) 843–854.
[11] B. Wightman, I. Ha, G. Ruvkun, Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in *C. elegans*, Cell 75 (1993) 855–862.
[12] S. Griffiths-Jones, The microRNA registry, Nucleic Acids Res. 32 (Database Issue) (2004) D109–D111.
[13] A. Rodriguez, S. Griffiths-Jones, J.L. Ashurst, A. Bradley, Identification of mammalian microRNA host genes and transcription units, Genome Res. 14 (2004) 1902–1910.
[14] R.F. Ketting, S.E. Fischer, E. Bernstein, T. Sijen, G.J. Hannon, R.H. Plasterk, Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in *C. elegans*, Genes Dev. 15 (2001) 2654–2659.
[15] G. Hutvagner, M.J. Simard, C.C. Mello, P.D. Zamore PD, Sequence specific inhibition of small RNA function, PLoS Biol. 2 (2004) E98.
[16] S. Vasudevan, Y. Tong, J.A. Steitz, Switching from repression to activation: microRNAs can up-regulate translation, Science 318 (2007) 1931–1934.
[17] N.P. Tsai, Y.L. Lin, L.N. Wei, MicroRNA mir-346 targets the 5′-untranslated region of receptor-interacting protein 140 (RIP140) mRNA and up-regulates its protein expression, Biochem. J. 424 (2009) 411–418.
[18] B.P. Lewis, C.B. Burge, D.P. Bartel, Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets, Cell 120 (2005) 15–20.
[19] A. Krek, D. Grün, M.N. Poy, R. Wolf, L. Rosenberg, E.J. Epstein, P. MacMenamin, I. da Piedade, K.C. Gunsalus, M. Stoffel, N. Rajewsky, Combinatorial microRNA target predictions, Nat. Genet. 37 (2005) 495–500.
[20] Z.J. Rutnam, T.N. Wight, B.B. Yang, miRNAs regulate expression and function of extracellular matrix molecules, Matrix Biol. 32 (2013) 74–85.
[21] M. Esteller, Non-coding RNAs in human disease, Nat. Rev. Genet. 12 (2011) 861–874.
[22] N. Su, Y. Wang, M. Qian, M. Deng, Combinatorial regulation of transcription factors and microRNAs, BMC Syst. Biol. 4 (2010) 150.

[23] U. Lehmann, B. Hasemeier, M. Christgen, M. Müller, D. Römermann, F. Länger, H. Kreipe, Epigenetic inactivation of microRNA gene hsa-mir-9-1 in human breast cancer, J. Pathol. 214 (2008) 17–24.

[24] D. Lodygin, V. Tarasov, A. Epanchintsev, C. Berking, T. Knyazeva, H. Körner, P. Knyazev, J. Diebold, H. Hermeking, Inactivation of miR-34a by aberrant CpG methylation in multiple types of cancer, Cell Cycle 7 (2008) 2591–2600.

[25] M. Götte, C. Mohr, C.Y. Koo, C. Stock, A.K. Vaske, M. Viola, S.A. Ibrahim, S. Peddibhotla, Y.H. Teng, J.Y. Low, K. Ebnet, L. Kiesel, G.W. Yip, miR-145-dependent targeting of Junctional Adhesion Molecule A and modulation of fascin expression are associated with reduced breast cancer cell motility and invasiveness, Oncogene 29 (2010) 6569–6580.

[26] J. Filmus, M. Capurro, Glypican-3: a marker and a therapeutic target in hepatocellular carcinoma, FEBS J. 280 (2013) 2471–2476.

[27] S. Jalvy-Delvaille, M. Maurel, V. Majo, N. Pierre, S. Chabas, C. Combe, J. Rosenbaum, F. Sagliocco, C.F. Grosset, Molecular basis of differential target regulation by miR-96 and miR-182: the glypican-3 as a model, Nucleic Acids Res. 40 (2012) 1356–1365.

[28] H. Hassan, B. Greve, M.S. Pavao, L. Kiesel, S.A. Ibrahim, M. Götte, Syndecan-1 modulates β-integrin-dependent and interleukin-6-dependent functions in breast cancer cell adhesion, migration, and resistance to irradiation, FEBS J. 280 (2013) 2216–2227.

[29] V.C. Ramani, A. Purushothaman, M.D. Stewart, C.A. Thompson, I. Vlodavsky, J.L. Au, R.D. Sanderson, The heparanase/syndecan-1 axis in cancer: mechanisms and therapies, FEBS J. 280 (2013) 2294–2306.

[30] V. Nikolova, C.Y. Koo, S.A. Ibrahim, Z. Wang, D. Spillmann, R. Dreier, R. Kelsch, J. Fischgräbe, M. Smollich, L.H. Rossi, W. Sibrowski, P. Wülfing, L. Kiesel, G.W. Yip, M. Götte, Differential roles for membrane-bound and soluble syndecan-1 (CD138) in breast cancer progression, Carcinogenesis 30 (2009) 397–407.

[31] B.N. Hannafon, P. Sebastiani, A. de las Morenas, J. Lu, C.L. Rosenberg, Expression of microRNA and their gene targets are dysregulated in preinvasive breast cancer, Breast Cancer Res. 13 (2011) R24.

[32] S.A. Ibrahim, G.W. Yip, C. Stock, J.W. Pan, C. Neubauer, M. Poeter, D. Pupjalis, C.Y. Koo, R. Kelsch, R. Schüle, U. Rescher, L. Kiesel, M. Götte, Targeting of syndecan-1 by microRNA miR-10b promotes breast cancer cell motility and invasiveness via a Rho-GTPase- and E-cadherin dependent mechanism, Int. J. Cancer 131 (2012) E884–E896.

[33] L. Ma, J. Teruya-Feldstein, R.A. Weinberg, Tumour invasion and metastasis initiated by microRNA-10b in breast cancer, Nature 449 (2005) 682–688.

[34] L. Sun, W. Yan, Y. Wang, G. Sun, H. Luo, J. Zhang, X. Wang, Y. You, Z. Yang, N. Liu, MicroRNA-10b induces glioma cell invasion by modulating MMP-14 and uPAR expression via HOXD10, Brain Res. 1389 (2011) 9–18.

[35] Z. Kasza, P.F. Fuchs, C. Tamm, A.S. Eriksson, P. O'Callaghan, F. Heindryckx, D. Spillmann, E. Larsson, S. Le Jan, I. Eriksson, P. Gerwins, L. Kjellen, J. Kreuger, MicroRNA-24 suppression of N-deacetylase/N-sulfotransferase-1 (NDST1) reduces endothelial cell responsiveness to VEGFA, J. Biol. Chem. 288 (2013) 25956–25963.

[36] M.E. Pedersen, G. Snieckute, K. Kagias, C. Nehammer, H.A. Multhaupt, J.R. Couchman, R. Pocock, An epidermal microRNA regulates neuronal migration through control of the cellular glycosylation state, Science 341 (2013) 1404–1408.

[37] X. Yang, Z.J. Rutnam, C. Jiao, D. Wei, Y. Xie, J. Du, L. Zhong, B.B. Yang, An anti-let-7 sponge decoys and decays endogenous let-7 functions, Cell Cycle 11 (2012) 3097–3108.

[38] H. Porsch, B. Bernert, M. Mehić, A.D. Theocharis, C.H. Heldin, P. Heldin, Efficient TGFβ-induced epithelial-mesenchymal transition depends on hyaluronan synthase HAS2, Oncogene 32 (2013) 4355–4365.

[39] C. Gialeli, A.D. Theocharis, N.K. Karamanos, Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting, FEBS J 278 (1) (2011 Jan) 16–27.

[40] M. Götte, G.W. Yip, Heparanase, hyaluronan, and CD44 in cancers: a breast carcinoma perspective, Cancer Res. 66 (2006) 10233–10237.

[41] L. Bao, Y. Yan, C. Xu, W. Ji, S. Shen, G. Xu, Y. Zeng, B. Sun, H. Qian, L. Chen, M. Wu, C. Su, J. Chen, MicroRNA-21 suppresses PTEN and hSulf-1 expression and promotes hepatocellular carcinoma progression through AKT/ERK pathways, Cancer Lett. 337 (2013) 226–236.

[42] Y. Takei, M. Takigahira, K. Mihara, Y. Tarumi, K. Yanagihara, The metastasis-associated microRNA miR-516a-3p is a novel therapeutic target for inhibiting peritoneal dissemination of human scirrhous gastric cancer, Cancer Res. 71 (2011) 1442–1453.

[43] A. Meirovitz, R. Goldberg, A. Binder, A.M. Rubinstein, E. Hermano, M. Elkin, Heparanase in inflammation and inflammation-associated cancer, FEBS J. 280 (2013) 2307–2319.

[44] D. Tang, Q. Zhang, S. Zhao, J. Wang, K. Lu, Y. Song, L. Zhao, X. Kang, S. Xu, L. Tian, The expression and clinical significance of microRNA-1258 and heparanase in human breast cancer, Clin. Biochem. 46 (2013) 926–932.

[45] L. Zhang, P.S. Sullivan, J.C. Goodman, P.H. Gunaratne, D. Marchetti, MicroRNA-1258 suppresses breast cancer brain metastasis by targeting heparanase, Cancer Res. 71 (2011) 645–654.

[46] H. Liu, X. Chen, W. Gao, G. Jiang, The expression of heparanase and microRNA-1258 in human non-small cell lung cancer, Tumour Biol. 33 (2012) 1327–1334.

[47] Y.C. Chan, S. Roy, Y. Huang, S. Khanna, C.K. Sen, The microRNA miR-199a-5p down-regulation switches on wound angiogenesis by derepressing the v-ets erythroblastosis virus E26 oncogene homolog 1-matrix metalloproteinase-1 pathway, J. Biol. Chem. 287 (2012) 41032–41043.

[48] N. Liu, Q. Sun, J. Chen, J. Li, Y. Zeng, S. Zhai, P. Li, B. Wang, X. Wang, MicroRNA-9 suppresses uveal melanoma cell migration and invasion through the NF-kappaB1 pathway, Oncol. Rep. 28 (2012) 961–968.

[49] V. Schaeffer, K.M. Hansen, D.R. Morris, R.C. LeBoeuf, C.K. Abrass, RNA-binding protein IGF2BP2/IMP2 is required for laminin-beta2 mRNA translation and is modulated by glucose concentration, Am. J. Physiol. Renal Physiol. 303 (2012) F75–F82.

[50] P. Gandellini, V. Profumo, A. Casamichele, N. Fenderico, S. Borrelli, G. Petrovich, G. Santilli, M. Callari, M. Colecchia, S. Pozzi, M. De Cesare, M. Folini, R. Valdagni, R. Mantovani, N. Zaffaroni, miR-205 regulates basement membrane deposition in human prostate: implications for cancer development, Cell Death Differ. 19 (2012) 1750–1760.

[51] M. Maurel, N. Dejeans, S. Taouji, E. Chevet, C.F. Grosset, MicroRNA-1291-mediated silencing of IRE1alpha enhances glypican-3 expression, RNA 19 (2013) 778–788.

[52] H. Hu, S. Li, X. Cui, X. Lv, Y. Jiao, F. Yu, H. Yao, E. Song, Y. Chen, M. Wang, L. Lin, The overexpression of hypomethylated miR-663 induces chemotherapy resistance in human breast cancer cells by targeting heparin sulfate proteoglycan 2 (HSPG2), J. Biol. Chem. 288 (2013) 10973–10985.

[53] G. Alpini, S.S. Glaser, J.P. Zhang, H. Francis, Y. Han, J. Gong, A. Stokes, T. Francis, N. Hughart, L. Hubble, S.M. Zhuang, F. Meng, Regulation of placenta growth factor by microRNA-125b in hepatocellular cancer, J. Hepatol. 55 (2011) 1339–1345.

[54] K.C. Chen, Y.S. Wang, C.Y. Hu, W.C. Chang, Y.C. Liao, C.Y. Dai, S.H. Juo, OxLDL up-regulates microRNA-29b, leading to epigenetic modifications of MMP-2/MMP-9 genes: a novel mechanism for cardiovascular diseases, FASEB J. 25 (2011) 1718–1728.

[55] T. Kunej, D.J. Skok, S. Horvat, P. Dovc, Z. Jiang, The glypican 3-hosted murine mir717 gene: sequence conservation, seed region polymorphisms and putative targets, Int. J. Biol. Sci. 6 (2010) 769–772.

[56] E. Chiao, P. Fisher, L. Crisponi, M. Deiana, I. Dragatsis, D. Schlessinger, G. Pilia, A. Efstratiadis, Overgrowth of a mouse model of the Simpson–Golabi–Behmel syndrome is independent of IGF signaling, Dev. Biol. 243 (2002) 185–206.

[57] F.A. Karreth, P.P. Pandolfi, ceRNA cross-talk in cancer: when ce-bling rivalries go awry, Cancer Discov. 3 (2013) 1113–1121.

[58] Wight TN, Kinsella MG, Evanko SP, Potter-Perigo S, Merrilees MJ. Versican and the regulation of cell phenotype in disease. Biochim Biophys Acta. 2014 Jan 5. pii: S0304-4165(13)00557-6. http://dx.doi.org/10.1016/j.bbagen.2013.12.028. [Epub ahead of print].

[59] D.Y. Lee, T. Shatseva, Z. Jeyapalan, W.W. Du, Z. Deng, B.B. Yang, A 3′-untranslated region (3′UTR) induces organ adhesion by regulating miR-199a* functions, PLoS One 4 (2009) e4527.

[60] D.Y. Lee, Z. Jeyapalan, L. Fang, J. Yang, Y. Zhang, A.Y. Yee, M. Li, W.W. Du, T. Shatseva, B.B. Yang, Expression of versican 3′-untranslated region modulates endogenous microRNA functions, PLoS One 5 (2010) e13599.

[61] L. Fang, W.W. Du, X. Yang, K. Chen, A. Ghanekar, G. Levy, W. Yang, A.J. Yee, W.Y. Lu, J.W. Xuan, Z. Gao, F. Xie, C. He, Z. Deng, B.B. Yang, Versican 3′-untranslated region (3′-UTR) functions as a ceRNA in inducing the development of hepatocellular carcinoma by regulating miRNA activity, FASEB J. 27 (2013) 907–919.

[62] Z. Jeyapalan, Z. Deng, T. Shatseva, L. Fang, C. He, B.B. Yang, Expression of CD44 3′-untranslated region regulates endogenous microRNA functions in tumorigenesis and angiogenesis, Nucleic Acids Res. 39 (2011) 3026–3041.

[63] Z.J. Rutnam, B.B. Yang, The non-coding 3′ UTR of CD44 induces metastasis by regulating extracellular matrix functions, J. Cell Sci. 125 (2012) 2075–2085.

[64] A.D. Theocharis, S.S. Skandalis, G.N. Tzanakakis, N.K. Karamanos, Proteoglycans in health and disease: novel roles for proteoglycans in malignancy and their pharmacological targeting, FEBS J. 277 (2010) 3904–3923.

[65] L.Y. Bourguignon, C. Earle, G. Wong, C.C. Spevak, K. Krueger, Stem cell marker (Nanog) and Stat-3 signaling promote MicroRNA-21 expression and chemoresistance in hyaluronan/CD44-activated head and neck squamous cell carcinoma cells, Oncogene 31 (2012) 149–160.

[66] L.Y. Bourguignon, G. Wong, C. Earle, L. Chen, Hyaluronan–CD44v3 interaction with Oct4–Sox2–Nanog promotes miR-302 expression leading to self-renewal, clonal formation, and cisplatin resistance in cancer stem cells from head and neck squamous cell carcinoma, J. Biol. Chem. 287 (2012) 32800–32824.

[67] K.D. Gerson, V.S. Maddula, B.E. Seligmann, J.R. Shearstone, A. Khan, A.M. Mercurio, Effects of beta4 integrin expression on microRNA patterns in breast cancer, Biol. Open 1 (2012) 658–666.

[68] X. Yu, D.M. Cohen, C.S. Chen, miR-125b Is an adhesion-regulated microRNA that protects mesenchymal stem cells from anoikis, Stem Cells 30 (2012) 956–964.

[69] M. Götte, Syndecans in inflammation, FASEB J. 17 (2003) 575–591.

[70] X. Zhang, J. Xu, J. Wang, L. Gortner, S. Zhang, X. Wei, J. Song, Y. Zhang, Q. Li, Z. Feng, Reduction of MicroRNA-206 contributes to the development of bronchopulmonary dysplasia through up-regulation of fibronectin 1, PLoS One 8 (2013) e74750.

[71] S.W. Shan, D.Y. Lee, Z. Deng, T. Shatseva, Z. Jeyapalan, W.W. Du, Y. Zhang, J.W. Xuan, S.P. Yee, V. Siragam, B.B. Yang, MicroRNA MiR-17 retards tissue growth and represses fibronectin expression, Nat. Cell Biol. 11 (2009) 1031–1038.

[72] C. Piovan, D. Palmieri, G. Di Leva, L. Braccioli, P. Casalini, G. Nuovo, M. Tortoreto, M. Sasso, I. Plantamura, T. Triulzi, C. Taccioli, E. Tagliabue, M.V. Iorio, C.M. Croce, Oncosuppressive role of p53-induced miR-205 in triple negative breast cancer, Mol. Oncol. 6 (2012) 458–472.

[73] M. Mancini, G. Saintigny, C. Mahe, M. Annicchiarico-Petruzzelli, G. Melino, E. Candi, MicroRNA-152 and -181a participate in human dermal fibroblasts senescence acting on cell adhesion and remodeling of the extra-cellular matrix, Aging (Albany NY) 4 (2012) 843–853.

[74] M. Maurel, S. Jalvy, Y. Ladeiro, C. Combe, L. Vachet, F. Sagliocco, P. Bioulac-Sage, V. Pitard, H. Jacquemin-Sablon, J. Zucman-Rossi, B. Laloo, C.F. Grosset, A functional screening identifies five microRNAs controlling glypican-3: role of miR-1271 down-regulation in hepatocellular carcinoma, Hepatology 57 (2013) 195–204.

[75] N. Huang, J. Lin, J. Ruan, N. Su, R. Qing, F. Liu, B. He, C. Lv, D. Zheng, R. Luo, MiR-219-5p inhibits hepatocellular carcinoma cell proliferation by targeting glypican-3, FEBS Lett. 586 (2012) 884–891.

[76] H.L. Miao, C.J. Lei, Z.D. Qiu, Z.K. Liu, R. Li, S.T. Bao, M.Y. Li, MicroRNA-520c-3p inhibits hepatocellular carcinoma cell proliferation and invasion through induction of cell apoptosis by targeting glypican-3, Hepatol. Res. (2013), http://dx.doi.org/10.1111/hepr.12121(Epub ahead of print).

[77] C. Feng, J. Li, J. Ruan, K. Ding, MicroRNA-125a inhibits cell growth by targeting glypican-4, Glycoconj. J. 29 (2012) 503–511.

[78] S. Yamanaka, A.V. Olaru, F. An, D. Luvsanjav, Z. Jin, R. Agarwal, C. Tomuleasa, I. Popescu, S. Alexandrescu, S. Dima, M. Chivu-Economescu, E.A. Montgomery, M. Torbenson, S.J. Meltzer, F.M. Selaru, MicroRNA-21 inhibits Serpini1, a gene with novel tumour suppressive effects in gastric cancer, Dig. Liver Dis. 44 (2012) 589–596.

[79] J.P. Myers, M. Santiago-Medina, T.M. Gomez, Regulation of axonal outgrowth and pathfinding by integrin–ECM interactions, Dev. Neurobiol. 71 (2011) 901–923.

[80] L.E. Stephens, A.E. Sutherland, I.V. Klimanskaya, A. Andrieux, J. Meneses, R.A. Pedersen, C.H. Damsky, Deletion of beta 1 integrins in mice results in inner cell mass failure and peri-implantation lethality, Genes Dev. 9 (1995) 1883–1895.

[81] E.L. George, E.N. Georges-Labouesse, R.S. Patel-King, H. Rayburn, R.O. Hynes, Defects in mesoderm, neural tube and vascular development in mouse embryos lacking fibronectin, Development 119 (1993) 1079–1091.

[82] G.W. Yip, M. Smollich, M. Götte, Therapeutic value of glycosaminoglycans in cancer, Mol. Cancer Ther. 5 (2006) 2139–2148.

[83] G. Li, C. Luna, J. Qiu, D.L. Epstein, P. Gonzalez, Targeting of integrin beta1 and kinesin 2alpha by microRNA 183, J. Biol. Chem. 285 (2010) 5461–5471.

[84] S. Hunt, A.V. Jones, E.E. Hinsley, S.A. Whawell, D.W. Lambert, MicroRNA-124 suppresses oral squamous cell carcinoma motility by targeting ITGB1, FEBS Lett. 585 (2011) 187–192.

[85] C.H. Wang, D.Y. Lee, Z. Deng, Z. Jeyapalan, S.C. Lee, S. Kahai, W.Y. Lu, Y. Zhang, B.B. Yang, MicroRNA miR-328 regulates zonation morphogenesis by targeting CD44 expression, PLoS One 3 (2008) e2420.

[86] E. Pantazaka, and E. Papadimitriou, Chondroitin sulfate-cell membrane effectors as regulators of growth -mediated vascular and cancer cell migration, BBA - General Subjects, in press, available online January 8, 2014.

[87] F. Denhez, S.A. Wilcox-Adelman, P.C. Baciu, S. Saoncella, S. Lee, B. French, W. Neveu, P.F. Goetinck, Syndesmos, a syndecan-4 cytoplasmic domain interactor, binds to the focal adhesion adaptor proteins paxillin and Hic-5, J. Biol. Chem. 277 (2002) 12270–12274.

[88] H. Ch. Lim, and J.R. Couchman, Syndecan-2 regulation of morphology in breast carcinoma cells is dependent on RhoGTPases, BBA - General subjects, in press, available online 18 January 2014.

[89] Q.K. Chen, K. Lee, D.C. Radisky, C.M. Nelson, Extracellular matrix proteins regulate epithelial-mesenchymal transition in mammary epithelial cells, Differentiation 86 (2013) 126–132.

[90] S.F. Tavazoie, C. Alarcon, T. Oskarsson, D. Padua, Q. Wang, P.D. Bos, W.L. Gerald, J. Massague, Endogenous human microRNAs that suppress breast cancer metastasis, Nature 451 (2008) 147–152.

[91] C. Chen, C.Q. Wu, Z.Q. Zhang, D.K. Yao, L. Zhu, Loss of expression of miR-335 is implicated in hepatic stellate cell migration and activation, Exp. Cell Res. 317 (2011) 1714–1725.

[92] X. Wang, G. Hu, J. Zhou, Repression of versican expression by microRNA-143, J. Biol. Chem. 285 (2010) 23241–23250.

[93] A. Domogatskaya, S. Rodin, K. Tryggvason, Functional diversity of laminins, Annu. Rev. Cell Dev. Biol. 28 (2012) 523–553.

[94] T. Kinoshita, N. Nohata, T. Hanazawa, N. Kikkawa, N. Yamamoto, H. Yoshino, T. Itesako, H. Enokida, M. Nakagawa, Y. Okamoto, N. Seki, Tumour-suppressive microRNA-29s inhibit cancer cell migration and invasion by targeting laminin–integrin signalling in head and neck squamous cell carcinoma, Br. J. Cancer 109 (2013) 2636–2645.

[95] A. Fowler, D. Thomson, K. Giles, S. Maleki, E. Mreich, H. Wheeler, P. Leedman, M. Biggs, R. Cook, N. Little, B. Robinson, K. McDonald, miR-124a is frequently down-regulated in glioblastoma and is involved in migration and invasion, Eur. J. Cancer 47 (2011) 953–963.

[96] K. Augoff, M. Das, K. Bialkowska, B. McCue, E.F. Plow, K. Sossey-Alaoui, miR-31 is a broad regulator of β1-integrin expression and function in cancer cells, Mol. Cancer Res. 9 (2011) 1500–1508.

[97] S. Valastyan, A. Chang, N. Benaich, F. Reinhardt, R.A. Weinberg, Concurrent suppression of integrin alpha5, radixin, and RhoA phenocopies the effects of miR-31 on metastasis, Cancer Res. 70 (2010) 5147–5154.

[98] A.D. Bradshaw, Diverse biological functions of the SPARC family of proteins, Int. J. Biochem. Cell Biol. 44 (2012) 480–488.

[99] K.D. Gerson, J.R. Shearstone, V.S. Maddula, B.E. Seligmann, A.M. Mercurio, Integrin β4 regulates SPARC protein to promote invasion, J. Biol. Chem. 287 (2012) 9835–9844.

[100] J.C. Henry, J.K. Park, J. Jiang, J.H. Kim, D.M. Nagorney, L.R. Roberts, S. Banerjee, T.D. Schmittgen, miR-199a-3p targets CD44 and reduces proliferation of CD44 positive hepatocellular carcinoma cell lines, Biochem. Biophys. Res. Commun. 403 (2010) 120–125.

[101] J. Liu, A. van Mil, E.N. Aguor, S. Siddiqi, K. Vrijsen, S. Jaksani, C. Metz, J. Zhao, G.J. Strijkers, P.A. Doevendans, J.P. Sluijter, MiR-155 inhibits cell migration of human cardiomyocyte progenitor cells (hCMPCs) via targeting of MMP-16, J. Cell. Mol. Med. 16 (2012) 2379–2386.

[102] Z. Jianwei, L. Fan, L. Xiancheng, B. Enzhong, L. Shuai, L. Can, MicroRNA 181a improves proliferation and invasion, suppresses apoptosis of osteosarcoma cell, Tumour Biol. 34 (2013) 3331–3337.

[103] D. Wu, P. Huang, L. Wang, Y. Zhou, H. Pan, P. Qu, MicroRNA-143 inhibits cell migration and invasion by targeting matrix metalloproteinase 13 in prostate cancer, Mol. Med. Rep. 8 (2013) 626–630.

[104] M. Adammek, B. Greve, N. Kässens, C. Schneider, K. Brüggemann, A.N. Schüring, A. Starzinski-Powitz, L. Kiesel, M. Götte, MicroRNA miR-145 inhibits proliferation, invasiveness, and stem cell phenotype of an in vitro endometriosis model by targeting multiple cytoskeletal elements and pluripotency factors, Fertil. Steril. 99 (2013)(1346-1355.e5).

[105] B. Greve, R. Kelsch, K. Spaniol, H.T. Eich, M. Götte, Flow cytometry in cancer stem cell analysis and separation, Cytometry A 81 (2012) 284–293.

[106] M. Götte, Endometrial cells get side-tracked: side population cells promote epithelial–mesenchymal transition in endometrial carcinoma, Am. J. Pathol. 176 (2010) 25–28.

[107] L. Gasimli, A. M. Hickey, B. Yang, G. Li, M. dela Rosa, A. V. Nairn, M. J. Kulik, J. S. Dordick, K. W. Moremen, S. Dalton, and R. J. Linhardt, Changes in glycosaminoglycan structure on differentiation of human embryonic stem cells towards mesoderm and endoderm lineages, BBA - General subjects, in press, available online 9 January 2014.

[108] F. Gattazzo, A. Urciuolo, and P. Bonaldo, Extracellular matrix: A dynamic microenvironment for stem cell niche, BBA - General subjects, in press, available online 10 January 2014.

[109] A. Wade, A. McKinney, and J. J. Phillips, Matrix regulators in neural stem cells functions, BBA - General Subjects, in press, available online 18 January 2014.

[110] J. Song, D. Kim, E.J. Jin, MicroRNA-488 suppresses cell migration through modulation of the focal adhesion activity during chondrogenic differentiation of chick limb mesenchymal cells, Cell Biol. Int. 35 (2011) 179–185.

[111] K. Sumiyoshi, S. Kubota, T. Ohgawara, K. Kawata, T. Nishida, T. Shimo, T. Yamashiro, M. Takigawa, Identification of miR-1 as a micro RNA that supports late-stage differentiation of growth cartilage cells, Biochem. Biophys. Res. Commun. 402 (2010) 286–290.

[112] K. Sumiyoshi, S. Kubota, T. Ohgawara, K. Kawata, T. Abd El Kader, T. Nishida, N. Ikeda, T. Shimo, T. Yamashiro, M. Takigawa, Novel role of miR-181a in cartilage metabolism, J. Cell. Biochem. 114 (2013) 2094–2100.

[113] B. Gradus, I. Alon, E. Hornstein, miRNAs control tracheal chondrocyte differentiation, Dev. Biol. 360 (2011) 58–65.

[114] O. Tang, X.M. Chen, S. Shen, M. Hahn, C.A. Pollock, MiRNA-200b represses transforming growth factor-beta1-induced EMT and fibronectin expression in kidney proximal tubular cells, Am. J. Physiol. Renal Physiol. 304 (2013) F1266–F1273.

[115] X. Kong, G. Li, Y. Yuan, Y. He, X. Wu, W. Zhang, Z. Wu, T. Chen, W. Wu, P.E. Lobie, T. Zhu, MicroRNA-7 inhibits epithelial-to-mesenchymal transition and metastasis of breast cancer cells via targeting FAK expression, PLoS One 7 (2012) e41523.

[116] C. Neubauer, L. Kiesel, M. Götte, MicroRNAs and the pathogenesis of endometriosis, J. Endometriosis 4 (2012) 1–16.

[117] A.C. Rapraeger, Synstatin: a selective inhibitor of the syndecan-1-coupled IGF1R-αvβ3 integrin complex in tumorigenesis and angiogenesis, FEBS J. 280 (2013) 2207–2215.

[118] B. Bauvois, New facets of matrix metalloproteinases MMP-2 and MMP-9 as cell surface transducers: outside-in signaling and relationship to tumor progression, Biochim. Biophys. Acta 1825 (2012) 29–36.

[119] L. Fang, Z. Deng, T. Shatseva, J. Yang, C. Peng, W.W. Du, A.J. Yee, L.C. Ang, C. He, S.W. Shan, B.B. Yang, MicroRNA miR-93 promotes tumor growth and angiogenesis by targeting integrin-beta8, Oncogene 30 (2011) 806–821.

[120] F. Leonhardt, S. Grundmann, M. Behe, F. Bluhm, R.A. Dumont, F. Braun, M. Fani, K. Riesner, G. Prinz, A.K. Hechinger, U.V. Gerlach, H. Dierbach, O. Penack, A. Schmitt-Graff, J. Finke, W.A. Weber, R. Zeiser, Inflammatory neovascularization during graft-versus-host disease is regulated by alphav integrin and miR-100, Blood 121 (2013) 3307–3318.

[121] A. Bonauer, G. Carmona, M. Iwasaki, M. Mione, M. Koyanagi, A. Fischer, J. Burchfield, H. Fox, C. Doebele, K. Ohtani, E. Chavakis, M. Potente, M. Tjwa, C. Urbich, A.M. Zeiher, S. Dimmeler, MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice, Science 324 (2009) 1710–1713.

[122] J.H. Fang, H.C. Zhou, C. Zeng, J. Yang, Y. Liu, X. Huang, J.P. Zhang, X.Y. Guan, S.M. Zhuang, MicroRNA-29b suppresses tumor angiogenesis, invasion, and metastasis by regulating matrix metalloproteinase 2 expression, Hepatology 54 (2011) 1729–1740.

[123] D.G. Seidler, N.A. Mohamed, C. Bocian, A. Stadtmann, S. Hermann, K. Schäfers, M. Schäfers, R.V. Iozzo, A. Zarbock, M. Götte, The role for decorin in delayed-type hypersensitivity, J. Immunol. 187 (2011) 6108–6119.

[124] R. Merline, K. Moreth, J. Beckmann, M.V. Nastase, J. Zeng-Brouwers, J.G. Tralhao, P. Lemarchand, J. Pfeilschifter, R.M. Schaefer, R.V. Iozzo, L. Schaefer, Signaling by the matrix proteoglycan decorin controls inflammation and cancer through PDCD4 and MicroRNA-21, Sci. Signal. 4 (2011) ra75.

[125] C. Schneider, N. Kassens, B. Greve, H. Hassan, A.N. Schuring, A. Starzinski-Powitz, L. Kiesel, D.G. Seidler, M. Gotte, Targeting of syndecan-1 by micro-ribonucleic acid miR-10b modulates invasiveness of endometriotic cells via dysregulation of the proteolytic milieu and interleukin-6 secretion, Fertil. Steril. 99 (2013)(871-881.e1).

[126] S.W. Jones, G. Watkins, N. Le Good, S. Roberts, C.L. Murphy, S.M. Brockbank, M.R. Needham, S.J. Read, P. Newham, The identification of differentially expressed microRNA in osteoarthritic tissue that modulate the production of TNF-alpha and MMP13, Osteoarthritis Cartilage 17 (2009) 464–472.

[127] S.J. Park, E.J. Cheon, M. Lee, H.A. Kim, MicroRNA-127-5p regulates matrix metalloproteinase-13 expression and IL-1beta-induced catabolic effects in human chondrocytes, Arthritis Rheum. 65 (2013) 3141–3152.

[128] Z.J. Liang, H. Zhuang, G.X. Wang, Z. Li, H.T. Zhang, T.Q. Yu, B.D. Zhang, MiRNA-140 is a negative feedback regulator of MMP-13 in IL-1beta-stimulated human articular chondrocyte C28/I2 cells, Inflamm. Res. 61 (2012) 503–509.
[129] J. Liu, J. Huang, Y. He, B. Liao, G. Liao, Genetic variants in the integrin gene predicted microRNA-binding sites were associated with the risk of prostate cancer, Mol. Carcinog. (2012), http://dx.doi.org/10.1002/mc.21973(Epub ahead of print).
[130] A. Brendle, H. Lei, A. Brandt, R. Johansson, K. Enquist, R. Henriksson, K. Hemminki, P. Lenner, A. Forsti, Polymorphisms in predicted microRNA-binding sites in integrin genes and breast cancer: ITGB4 as prognostic marker, Carcinogenesis 29 (2008) 1394–1399.
[131] X.Y. Liu, Q.S. Tang, H.C. Chen, X.L. Jiang, H. Fang, Lentiviral miR30-based RNA interference against heparanase suppresses melanoma metastasis with lower liver and lung toxicity, Int. J. Biol. Sci. 9 (2013) 564–577.
[132] J. Elmen, M. Lindow, S. Schutz, M. Lawrence, A. Petri, S. Obad, M. Lindholm, M. Hedtjarn, H.F. Hansen, U. Berger, S. Gullans, P. Kearney, P. Sarnow, E.M. Straarup, S. Kauppinen, LNA-mediated microRNA silencing in non-human primates, Nature 452 (2008) 896–899.
[133] R.E. Lanford, E.S. Hildebrandt-Eriksen, A. Petri, R. Persson, M. Lindow, M.E. Munk, S. Kauppinen, H. Orum, Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection, Science 327 (2010) 198–201.
[134] J.S. Zawistowski, K. Nakamura, J.S. Parker, D.A. Granger, B.T. Golitz, G.L. Johnson, MicroRNA 9-3p targets beta1 integrin to sensitize claudin-low breast cancer cells to MEK inhibition, Mol. Cell. Biol. 33 (2013) 2260–2274.
[135] E. van Rooij, E.N. Olson, MicroRNA therapeutics for cardiovascular disease: opportunities and obstacles, Nat. Rev. Drug Discov. 11 (2012) 860–872.