The role of microRNAs in arterial remodelling

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Summary
Adaptive alterations of the vessel wall architecture, called vascular remodelling, can be found in arterial hypertension, during the formation of aneurysms, in restenosis after vascular interventions, and in atherosclerosis. MicroRNAs (miR) critically affect the main cellular players in arterial remodelling and may either promote or inhibit the structural changes in the vessel wall. They regulate the phenotype of smooth muscle cells (SMCs) and control the inflammatory response in endothelial cells and macrophages. In SMCs, different sets of miRs induce either a synthetic or contractile phenotype, respectively. The conversion into a synthetic SMC phenotype is a crucial event in arterial remodelling. Therefore, reprogramming of the SMC phenotype by miR targeting can modulate the remodelling process. Furthermore, the effects of stimuli that induce remodelling, such as shear stress, angiotensin II, oxidised low-density lipoprotein, or apoptosis, on endothelial cells are mediated by miRs. The endothelial cell-specific miR-126, for example, is transferred in microvesicles from apoptotic endothelial cells and plays a protective role in atherogenesis. The inflammatory response of the innate immune system, especially through macrophages, promotes arterial remodelling. miR-155 induces the expression of inflammatory cytokines, whereas miR-146a and miR-147 are involved in the resolution phase of inflammation. However, in vivo data on the role of miRs in vascular remodelling are still scarce, which are required to test the therapeutic potential of the available, highly effective miR inhibitors.

Keywords
Atherosclerosis, macrophage, smooth muscle cells, vascular remodelling

Introduction
The structure of a blood vessel wall is closely related to its functional requirements and thus is highly specialised in different parts of the circulatory system. Adaptive alterations of the vessel wall architecture, called vascular remodelling, may occur in response to a diverse array of stimuli, such as pressure, flow, or injury. For instance, the size of the tunica media may increase due to arterial hypertension and decrease during the formation of aneurysms. Furthermore, neointimal lesion formation may occur, as in restenosis after stent implantation or in atherosclerosis (1). Thus, structural adaptions of the vessel wall to environmental stress can promote disease development or constitute a medical condition on its own. Vascular remodelling is driven by all vascular cell types, including endothelial cells and smooth muscle cells (SMCs), and involves the reconstruction of the extracellular matrix (ECM). Furthermore, inflammatory cell recruitment, particularly of monocytes and macrophages, plays a crucial role in vascular remodelling by regulating SMC function and ECM turnover (2).

MicroRNAs (miRs) are non-coding, small RNAs (~22 nt) that regulate gene expression at a post-transcriptional level through translational repression or mRNA decay (3). Specific sets of these miRs play key roles in determining cell fate and tissue homeostasis including in SMCs and endothelial cells (4, 5). Thus, miRs critically regulate the phenotype of cell types involved in vascular remodelling. Identification of miRs that have specific functions in vascular remodelling promises to reveal a completely new class of targets in the treatment and prevention of vascular diseases. In this review, we summarise the current evidence for the contribution of miRs in vascular remodelling and atherosclerosis.

MiRs drive phenotypic changes of SMCs
SMCs show remarkable plasticity under various disease conditions, oscillating between a contractile and synthetic phenotype, although the specific impact of the separate phenotypes on vascular diseases is unclear (6). Synthetic SMCs are characterised by a reduced contractile protein content, an increased rate of proliferation, and increased secretion of extracellular matrix proteins and cytokines (7). In vitro platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β/bone morphogenetic protein (BMP) pathways control the SMC phenotype (8). Whereas PDGF signalling promotes the proliferative and synthetic phenotype, activation of TGF-β/BMP pathways favour their differentiation into contractile SMCs. In atherosclerotic lesions and neointimal tissue, most SMCs display a synthetic phenotype and are the
primary cell type involved in vascular repair following different types of injuries.

The development of SMCs is dependent on the functional expression of miRs. Absence of the miR processing enzyme Dicer in SMCs during development leads to late embryonic lethality and haemorrhage, most likely due to impaired proliferation and differentiation of SMCs (9). Mice with postnatal loss of Dicer expression show a reduced number of SMCs in the vessel wall and concomitantly a diminished thickness of the media. Furthermore, the expression of contractile proteins is impaired in Dicer-deficient SMCs in vivo, which may explain their lower arterial blood pressure (10).

MiR-145 is one of the most highly expressed miRs in SMCs and has been found to regulate the SMC phenotype by up-regulation of SMC-specific proteins, such as calponin and smooth muscle myosin heavy chain, in vitro (11). Moreover, introduction of miR-145 triggers reprogramming of fibroblasts and human embryonic stem cells into SMCs (12, 13). While genetic deletion of miR-145 does not impair embryonic development and is not associated with reduced SMC marker expression, it is associated with impaired stress fiber expression, indicating disturbed actin cytoskeleton dynamics (14). Noticeably, the absence of miR-145 reduces the vessel wall thickness and lowers blood pressure due to hypotrophy of SMCs (14). MiR-145 is down-regulated following vascular injury, during atherosclerosis, and in experimentally induced aneurysms (11, 12, 15). Local overexpression of miR-145 has been shown to increase SMC marker expression and diminish neointima formation, indicating a protective role of miR-145 in vascular remodelling (11, 15). However, neointimal hyperplasia following carotid ligation is attenuated in miR-145 deficient mice (11, 12, 14). Multiple targets of miR-145 have been identified that are involved in SMC differentiation and actin cytoskeleton dynamics, such as KLF5, KLF4, calmodulin kinase, myocardin-related transcription factor (MRTF)-B, myocardin, and angiotensin converting enzyme (ACE) (11, 12, 14, 16) (Fig. 1). Apart from phenotypic modulation, miR-145 inhibits the PDGF-induced proliferation of SMCs in vitro, demonstrating an important role for miR-145 in the proliferative response of SMCs (11, 12).

MiR-145 is expressed along with miR-143 from a common bicistronic precursor and both are transcriptionally regulated by myocardin, the serum response factor (SRF), and Nkx2-5 (12, 14). Accordingly, miR-143 is also highly expressed in muscularised arteries. Three different miR-143/145-/- strains of mice that were independently generated by different groups show thinning of their arterial walls and reduced arterial blood pressure (14–16). Furthermore, diminished expression of SMC-specific proteins in the aorta was found in two of the miR-143/-/145/- mouse lines (15, 16). Interestingly, aged miR-143/145/-/- mice spontaneously develop macrophage-rich neointimal lesions even in the absence of vascular injury or hyperlipidaemia (16). This effect may be due to increased expression of angiotensin-converting enzyme (ACE) in the miR-143/145-deficient mice, which results in increased angiotensin II generation in the vessel wall (16). Selective knock out of miR-143 does not lead to a substantial thinning of the vessel wall but does reduce neointima formation by 60% following carotid ligation (14). This effect may be explained by the observation that inhibition of miR-143 increases the proliferation rate of SMCs in vitro, probably through up-regulation of Elk-1 (12). In addition, induction of miR-143 by SRF in SMCs represses the transcription factor FRA-1, which regulates the expression of the miR-21 (17). Down-regulation of FRA-1 by miR-143 abrogates the miR-21-dependent repression of PTEN, which results in a less proliferative SMC phenotype (17). Interestingly, the transfer of miR-143 and miR-145 from endothelial cells to SMCs via microvesicles reduces atherosclerosis and promotes a contractile SMC phenotype (18).

MiR-1 is also induced during SMC differentiation and increases the expression of SMC-specific contractile proteins by targeting KLF4 (19, 20) (Fig. 1). Furthermore, myocardin-induced miR-1 expression is centrally involved in myocardin-dependent SMC marker synthesis, contractility, and proliferation (20, 21). During neointima formation, miR-1 is down-regulated and expression of the oncogenic serine/threonine kinase Pim-1, a direct target of miR-1 in SMCs, increases (21). However, it remains unknown whether Pim-1 mediates the effects of miR-1 on SMC proliferation and how miR-1 affects neointima formation.

Another highly expressed miR in the vasculature is miR-133, which is down-regulated after vascular injury and in proliferating SMCs (22). MiR-133 impairs the proliferation of SMCs and inhibits the PDGF-induced switch towards a synthetic SMC phenotype by repressing the transcription factor Sp-1 (22) (Fig. 1). Accordingly, overexpression of miR-133 in injured arteries decreases neointima formation and reduces the proliferation of SMCs (22).

De-differentiation of SMCs in vitro by serum starvation results in the differential regulation of 135 miRs, including upregulation of miR-26a (23). Differentiation of SMCs is most likely impaired by miR-26a via repression of SMAD-1, which alters TGF-β and BMP signalling (23). In contrast, the serum-induced proliferative response of SMCs is mediated by increased expression of miR-146a, which suppresses KLF4 (24). Inhibition of miR-146a reduces neointima formation and SMC proliferation after balloon injury (24).

MiR-21 is also highly up-regulated following balloon injury and carotid ligation and promotes neointima formation (25, 26). Inhibition of miR-21 decreases SMC proliferation and increases the apoptosis of SMCs. These effects are associated with miR-21-induced activation of the Akt pathway via suppression of PTEN and upregulation of Bcl-2 expression (26) (Fig. 1). Interestingly, miR-21 is induced by BMP4 and TGF-β and increases the biosynthesis of contractile proteins in SMCs through suppression of programmed cell death 4 (PDCD4) (27), suggesting a role for miR-21 in SMC differentiation. However, miR-21 expression is also up-regulated in dedifferentiated SMCs and represses SMC differentiation markers (25, 26). Therefore, the role of miR-21 in the differentiation of SMCs is controversial, and further studies are needed to address its role in the phenotypic modulation of SMCs.

In addition, miR-221 and miR-222 are induced by vascular injury and increase neointima formation through targeting the tu-
mourn suppressors and cell cycle inhibitors p27(Kip1) and p57(Kip2), which results in enhanced proliferation of SMCs (28). De-differentiation of SMCs via PDGF is mediated by miR-221-induced repression of c-kit and p27(Kip1) (29). miR-24 is also induced in PDGF-treated SMCs and impairs TGF-β/BMP signalling by repression of Tribbles-like protein-3 (Trb3) and SMAD proteins (30). Therefore, miR-24 may be a crucial regulator of the crosstalk between PDGF and TGF-β/BMP signalling that is essential for the PDGF-induced phenotype switch towards synthetic SMCs (Fig. 1).

MiR-31 is also abundantly expressed in SMCs and up-regulated during proliferation of SMCs and neointima formation (31). Inhibition of miR-31 reduces the proliferation of SMCs in vitro and in neointima by targeting large tumor suppressor homolog 2 (Lats2) (31). Therefore, miR-31, miR-221, miR-222, and miR-21 constitute a miR network that promotes SMC proliferation (Fig. 1). In summary, miR networks tightly control proliferation and differentiation in SMCs and critically affect the response of SMCs upon vascular injury.

MiRs modulate the stress response of endothelial cells

Endothelial cells are located at the interface between the circulation and the vessel wall. Therefore, they are perfectly located to sense remodelling-inducing stimuli, such as haemodynamic stress or hyperlipidaemia as well as trigger the vascular response to these stimuli as an effector cell type.

MiR-126 is not only specifically expressed in endothelial cells but is also one of the most abundant endothelial miRs (32, 33). Binding sites have been identified in the putative promoter region of miR-126 for several transcription factors such as E26 transformation-specific sequences (ETS) factor and KLF2, which positively regulate the expression of miR-126 (34, 35). Targeted deletion or knock-down of miR-126 causes vascular leakage during embryonic development and impairs neovascularisation after myocardial infarction due to increased expression of miR-126 targets and inhibitors of VEGF signalling SPRED1 and PIK3RS (33, 36). Furthermore, miR-126 reduces leukocyte adhesion to endothelial cells by suppressing the expression of VCAM-1, suggesting a crucial role in vascular inflammation (32).

Endothelial cell apoptosis upon exposure to noxious cues is a critical event in several forms of arterial remodelling, e.g. in pulmonary hypertension and in disturbed flow-induced atherogenesis (37). Interestingly, miR-126 is selectively enriched in microvesicles released from apoptotic endothelial cells. These apoptotic microvesicles shuttle miR-126 to distant cells as a messenger signal that up-regulates the chemokine CXCL12 via activation of an autoregulatory feedback loop by regulator of G-protein signalling 16 (RGS16)-mediated induction of the CXCL12 receptor CXCR4 (38). This may explain why increased miR-126 expression promotes a more stable plaque phenotype with reduced macrophage

![Figure 1: Phenotype-specific gene expression in SMCs is mediated by miRs. Synthetic and contractile SMCs are characterised by increased expression of a specific set (network) of miRs that either inhibit or promote the proliferation and/or expression of contractile proteins. Lats2, large tumour suppressor homolog 2; Trb3, Tribbles-like protein-3; myoc, myocardin; CalmK, calmodulin K; MRTF-B, myocardin-related transcription factor-B; KLF4/5, Krüppel-like factor 4/5; FRA-1, Fos related antigen-1; PDCD4, programmed cell death 4; Sp-1, Sp1 transcription factor; ACE, angiotensin-converting enzyme; PTEN, phosphatase and tensin homolog; p57, cyclin-dependent kinase inhibitor 1C (CDKN1C); p27, cyclin-dependent kinase inhibitor 18 (CDKN1B); c-kit, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; ELK-1, ELK1 member of ETS oncogene family; PIM-1, proviral integration site 1.](image-url)
content but increased progenitor cell influx and SMC content (38).
In agreement with this protective role of miR-126 in experimental
models of atherosclerosis, miR-126 plasma levels were found to be
decreased in patients with coronary atherosclerosis and diabetes,
which can be explained by impaired packaging of miR-126 in
microvesicles (39, 40). Accordingly, miR-126 levels are elevated in
patients with acute coronary syndrome indicating enhanced secre-
tion of miR-126-loaded microvesicles (41). Furthermore, miR-126
levels decrease during transcoronary passage in patients with myo-
cardial damage, which may be related to increased delivery of
miR-126 to the culprit lesion (41). Therefore, microvesicles may
provide an important shuttle mechanism that allows the cell-to-
cell communication over a long distance by the delivery of miRs.

However, there is a binding site for miR-126 in the 3′-UTR of
CXCL12 mRNA, which mediates direct suppression of CXCL12 by
miR-126 in endothelial cells (38, 42). Inhibition of miR-126 is as-
associated with increased mobilisation of vascular progenitor cells,
probably via upregulation of CXCL12 (42). This suggests that
miR-126 can have opposing effects on CXCL12 expression de-
dependent on the binding preferences of miR-126 to either RGS16 or
CXCL12 and the availability of these two miR targets (Fig. 2).

Low endothelial shear stress (LSS) promotes the activation of
endothelial cells towards a proatherogenic phenotype and the
formation of atherosclerotic plaques at predilection sites like bifur-
cations or curvatures (43). Both LSS and anti-atherogenic high
shear stress (HSS) regulate gene expression in endothelial cells via
modulating expression of miRs (Fig. 2). MiR-10a is down-regu-
lated in endothelial cells from athero-susceptible regions of the aor-
tic arch and aortoareolar branches (44), which leads to activation of
the pro-inflammatory nuclear factor (NF)-κB pathway through in-
creased expression of the miR-10a targets mitogen-activated kinase
kinase 7 (MAP3K7) and β-transducin repeat-containing gene
(TRC) (44). Furthermore, HSS up-regulates miR-19a, which
suppresses endothelial cell proliferation by targeting cyclin D1 (45,
46). In contrast, miR-663 is induced by LSS and enhances the en-
dothelial adhesion of monocytes (47). There is conflicting evidence
for flow-mediated regulation of miR-21 in endothelial cells. HSS-
induced upregulation of miR-21 has been reported to drive athero-
protective NO production (46). However, LSS-induced miR-21 ex-
pression, which is characterised by enhanced VCAM-1– and
CCL2-dependent monocyte adhesion via suppression of PPAR-
α, has pro-inflammatory effects (48). In addition, LSS transcription-
ally activates the expression of the anti-angiogenic miR-17–92
cluster, including miR-92a, which targets KLF2, an important in-
hibitor of pro-inflammatory activation of endothelial cells (49).
Thus, miR-92a may promote the proatherogenic endothelial phe-
notype under disturbed flow through suppression of KLF2 and its
key targets eNOS and thrombomodulin (49). Moreover, since KLF2
is a transcriptional activator of miR-126, miR-92a may also control
the regulation of miR-126 by shear flow (34, 46, 49).

Figure 2: MiR networks in endothelial cells control the response to
haemodynamic stress and atherogenic stimuli. High shear stress (HSS)
is atheroprotective and up-regulates miRs that suppress endothelial prolifer-
ation and the inflammatory response. In contrast, low shear stress (LSS) in-
duces miRs that promote inflammatory gene expression by repressing anti-
flammatory transcription factors. Oxidised LDL (oxLDL)-induced apoptosis
of endothelial cells is mediated by miR-365. MiR-155 and miR-221 are in-
duced by angiotensin II (AngII) and inhibit the AngII-induced inflammatory
activation of endothelial cells. The transfer of miR-126 via microvesicles de-

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miR-155 is constitutively expressed in endothelial cells and also induced by HSS (46). By targeting the angiogenesis II type 1 receptor (AT1R) and Ets-1, miR-155 dampens the pro-inflammatory and migration-inducing effects of angiogenesis II on endothelial cells (50, 51). Similarly, miR-221 and miR-222 are highly expressed in endothelial cells and suppress the Ets-1-mediated inflammatory response in endothelial cells (50). Therefore, miR-155, miR-221, and miR-222 play important roles in restricting the pro-inflammatory response of endothelial cells upon angiogenesis II stimulation (Fig. 2).

Oxidised LDL (oxLDL) triggers pro-inflammatory activation and apoptosis of endothelial cells, thus critically regulating atherosclerosis. In vitro, oxLDL-induced endothelial apoptosis is associated with upregulation of several miRs, such as miR-365 and miR-142–5p (52). Interestingly, miR-365 mediates oxLDL-induced apoptosis by suppressing the anti-apoptotic factor Bcl2 (52). Therefore, targeting miR-365 to reduce endothelial apoptosis might inhibit the pro-atherogenic effects of oxLDL (Fig. 2).

Taken together, distinct functional subgroups of miRs have been identified that modulate the endothelial response in vascular remodelling. Either constitutively expressed miRs, such as miR-126, or miRs that are induced by anti-atherogenic stimuli, such as miR-10a, appear to be important in the prevention of atherosclerosis. In contrast, the pro-atherogenic effects of LSS or oxLDL are in part mediated by the upregulation of miRs, such as miR-663 and miR-365.

**MiRs control macrophage function involved in arterial remodelling**

Inflammation of the vessel wall is characterised by the infiltration of monocytes and macrophages and plays a causal role in arterial remodelling, resulting in arterial or pulmonary hypertension, formation of aneurysms, or atherosclerosis (53–55). The macrophage inflammatory response to various stimuli is characterised by the upregulation of an array of miRs, such as miR-155, miR-146, miR-147, miR-21, and miR-9 (56). OxLDL also induces substantial changes in the miR expression profile in monocytes and macrophages (57, 58). Although direct evidence for the contribution of miRs to the inflammatory activation of macrophages during arterial remodelling is currently lacking, many of the known functional aspects of miRs in macrophages may be relevant to this process.

MiR-146a and miR-146b differ by only two nucleotides and, although the respective genes are located on different chromosomes, stimulation of TLR-2, TLR-4, and TLR-5 strongly induces both miRs in macrophages by activation of NF-κB (59). Up-regulation of miR-146a/b activates a negative feedback loop through repression of interleukin (IL)-1 receptor-associated kinase 1 (IRAK1) and tumour necrosis factor (TNF)-receptor-associated factor 6 (TRAF6) that limits inflammatory Toll-like and cytokine signalling, conveying lipopolysaccharide (LPS) tolerance of monocytes (59, 60) (Fig. 3). Both miR-146a and miR-146b are up-regulated after stimulation with oxLDL in primary human monocytes (58). However, in macrophages oxLDL-mediated suppression of miR-146a promotes lipid uptake and cytokine release, most likely due to reduced suppression of the miR-146a target TLR4 (57) (Fig. 3). Interestingly, miR-146a and -b are both up-regulated in human atherosclerotic plaques (61).

Similar to miR-146, miR-147 also limits the macrophage inflammatory response following TLR stimulation (62). Activation of TLR4 results in a much stronger induction of miR-147 compared to stimulation of TLR-2 or TLR3. The miR-147 promoter region contains functional binding sites for NF-κB and a GAS element required for LPS-induced miR-147 expression (62). TLR4 stimulation induces NF-κB and STAT1 binding to the miR-147 promoter via MyD88 and TRIF (62). Inhibition of TLR-induced miR-147 reduces the secretion of inflammatory cytokines, such as TNF-α and IL-6, from macrophages (62) (Fig. 3). Thus, the reduced level of miR-147 in peripheral monocytes from patients with coronary artery disease might exacerbate vascular inflammation during atherogenesis (63).

In addition, oxLDL up-regulates miR-125a-5p in primary human monocytes, and inhibition of miR-125a-5p increases lipid accumulation, likely due to enhanced expression of the scavenger receptors LOX-1 and CD68 (Fig. 3). Moreover, inhibition of miR-125a-5p increases the secretion of IL-6, TNF-α, IL-2, and TGF-β from oxLDL-treated monocytes (58). Although miR-125a-5p directly targets oxysterol-binding protein-like 9 (ORP9) in monocytes and macrophages, its functional role in oxLDL-stimulated monocytes remains unclear (58).

In macrophages, miR-155 is strongly up-regulated by activation of various TLRs via either MyD88– or TRIF-dependent signalling pathways (64). TLR4-induced miR-155 expression can be inhibited by IL-10 (65). The effect of oxLDL on miR-155 expression is controversial. Whereas upregulation of miR-155 by oxLDL has been found in monocytes and macrophages (58, 66), suppression of miR-155 has also been reported (57) (Fig. 3). These inconsistent results indicate that specific features of the respective LDL preparation, such as the degree of oxidation, may play a critical role in the regulation of miR-155. Mildly oxidised LDL (moxLDL) preferentially activates TLR4, which has not been described for profoundly oxidised LDL (67).

There is conflicting evidence for the functional role of miR-155 in the inflammatory activation of the macrophage lineage (Fig. 3). In monocyte-derived dendritic cells, miR-155 inhibits the production of IL-1β upon LPS stimulation and modulates the TLR/IL-1 signalling cascade by directly targeting TAB2, which is an intermediate in the IL-1 pathway that also activates JNK, p38, and NF-κB (68). Inhibition of miR-155 leads to up-regulation of pro-inflammatory mediators, such as IL1β, CCL5, and IL12. However, expression of molecules with anti-inflammatory functions, such as IL-10 and SOCS3, also increases following miR-155 inhibition (69). Silencing of oxLDL-induced miR-155 enhances lipid uptake, activates the NF-κB pathway, increases the expression of scavenger receptors, and promotes the secretion of several pro-inflammatory cytokines, which indicates negative feedback regulation by miR-155 (66) (Fig. 3).
Evidence for a pro-inflammatory role of miR-155 consists of the identification of Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP1), an important negative regulator of the PI3K/Akt pathway and TLR4 signalling, as a direct miR-155 target in macrophages (70). Accordingly, inhibition of miR-155 reduces the expression of TNF-α, IL-6, IL-17, IP-10, and CCL2 in LPS-stimulated macrophages through targeting of SOCS1 (71). Interestingly, Akt activation negatively regulates miR-155 expression, which appears to be required for endotoxin tolerance in vivo (71). Furthermore, miR-155 represses the IL13 receptor alpha1, resulting in reduced expression of IL-13-dependent genes, such as SOCS1, CCL18, and CD23, that are involved in the establishment of an M2 phenotype in macrophages (72). The TGF-β signalling pathway in macrophages is also affected by miR-155 through repression of SMAD2 (73), leading to reduced expression of IL-1β, MMP9, VEGF, ICAM-1, and DC-SIGN upon TGF-β stimulation (73). Even the basal level of IL-1β expression is reduced by knockdown of miR-155. In mitogen-activated protein kinase phosphatase-1 (MKP-1)-deficient macrophages, miR-155 expression is up-regulated, which leads to increased STAT1 activation and enhanced iNOS expression following LPS stimulation due to repression of SOCS-1 (74). Taken together, miR-155 is centrally involved in the fine-tuning of the macrophage inflammatory response, although its net effect seems dependent on the disease context (Fig. 3).

Interestingly, the levels of circulating miR-155 are significantly reduced in patients with coronary heart disease (40). Moreover, miR-155 plasma levels decline with age and are significantly higher in females compared with males (40). Microarray analysis has revealed that miR-155 is significantly up-regulated in human atherosclerotic plaques (61). These findings indicate that miR-155 is crucially involved in the development of human atherosclerosis.

Analogous to endothelial cells, miRs such as miR-150 can also be enriched in microvesicles derived from monocytes upon stimulation with LPS or H2O2. This active secretion in microvesicles contributes to increased miR-150 plasma levels and results in transfer of miR-150 to endothelial cells (75) (Fig. 3). Exogenous miR-150 targets c-myb and enhances endothelial cell migration (75). Fur-
thermore, patients with atherosclerosis have increased miR-150 content in circulating microvesicles (75). Interestingly, microvesicles are also released from monocytes and macrophages by cholesterol enrichment, which may result in increased levels of circulating microvesicles under hyperlipidaemia (76).

MiR networks regulate the response of macrophages towards inflammatory and atherogenic stimuli and may play an important role in the inflammatory response during vascular remodelling. However, some results from in vitro studies are conflicting and further investigations in animal models are required to define the function of macrophage-specific miRs in vascular remodelling and atherosclerosis.

Conclusion

MicroRNAs critically affect the main cellular players in arterial remodelling and atherogenesis. MiRs regulate the SMC phenotype following vascular injury and control the inflammatory response in endothelial cells and macrophages. Surprisingly, in vivo data on the role of miRs in vascular remodelling are still scarce, which are required to test the therapeutic potential of the available, highly effective miR inhibitors for cardiovascular diseases (77). These anti-miRs are antisense oligonucleotides with different types of chemical modifications which provide increased in vivo stability and cell permeability. Therefore, local application of anti-miRs via coated stents and systemic administration of anti-miRs might be a feasible therapeutic approach in vascular remodelling. In addition, many miRs appear to actually have beneficial properties, such as miR-126. However, miR mimics, like siRNAs, lack the favourable characteristics of anti-miRs in terms of in vivo application and require more elaborated delivery systems. In this regard, the endogenous microvesicle-based transfer of miRs might serve as a template for the development of effective miR carriers. An improved understanding of the exceptional plasma stability of miRs and development of cell-targeting delivery strategies are necessary for the implementation of this therapeutic strategy.

Conflicts of interest

None declared.

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