Vascular Pharmacology 114 (2019) 49–63

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Non-coding RNAs in vascular remodeling and restenosis

Ciro Indolfi[a,b,*], Claudio Iaconetti[a], Clarice Gareri[a], Alberto Polimeni[a], Salvatore De Rosa[a]

[a] Division of Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Italy
[b] URT CNR of IFC, University Magna Graecia, Italy

ARTICLE INFO

Keywords:
Restenosis
Noncoding RNA
Vascular remodeling
microRNAs

ABSTRACT

Vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) are crucial in vascular remodeling. They exert pivotal roles in the development and progression of atherosclerosis, vascular response to injury, and restenosis after transcatheter angioplasty.

As a witness of their importance in the cardiovascular system, a large body of evidence has accumulated about the role played by micro RNAs (miRNA) in modulating both VSMCs and ECs. More recently, a growing number of long noncoding RNA (lncRNAs) came beneath the spotlights in this research field. Several mechanisms have been revealed by which lncRNAs are able to exert a relevant biological impact on vascular remodeling.

The aim of this review is to provide an integrated summary of ncRNAs that exert a relevant biological function in VSMCs and ECs of the vascular wall, with emphasis on the available clinical evidence of the potential usefulness of these molecules as circulating biomarkers of in-stent restenosis.

1. Introduction

Over the last four decades, percutaneous coronary intervention (PCI) has revolutionized the field of coronary artery disease (CAD) [1]. Initially, high re-intervention rates were registered after PCI by means of sole balloon angioplasty, which were mostly related to early arterial recoil, the tendency of the vessel to revert to its original shape once deformed [2]. Coronary stents were introduced to overcome these limitations. Nevertheless, the use of stents brought about a new challenge, namely the ominous neointimal hyperplasia due to aberrant vascular smooth muscle cell (VSMCs) proliferation and migration after stent implantation [3,4]. The resulting luminal encroachment is responsible for in-stent restenosis (ISR), recurrent ischemia, and the need to repeat revascularization in up to 20% of patients treated with bare-metal stents (BMS) at 1 year [5,6]. Drug-eluting stents (DES) have been developed to prevent restenosis. In fact, DES are able to release an antiproliferative drug, which prevents cell proliferation and neointima formation. Several clinical trials confirmed a dramatic reduction in the rate of target lesion revascularization after PCI [7,8]. However, DES brought about a new threat: late stent thrombosis (ST) [9]. The increased risk for ST after DES implantation is related to the non-selective effect exerted by the antiproliferative drugs eluted. These are very effective in inhibiting VSMCs proliferation and migration, but are also responsible for a relevant side effect: inhibition of re-endothelialization, leading to a prolonged exposition of pro-thrombotic surfaces to the bloodstream [10].

Altogether, these biological processes, mostly involving VSMCs and ECs, but also lymphocytes, monocytes, macrophages and platelets constitute vascular remodeling and represent the common biological and pathophysiological ground for the progression of atherosclerosis, of vascular response to chronic injury as happens with diabetes or hypertension, up to the genesis of ISR [11].

Abbreviations: VSMCs, Vascular smooth muscle cells; ECs, endothelial cells; lncRNAs, long noncoding RNA; miRNA, micro RNA; PCI, percutaneous coronary intervention; CAD, coronary artery disease; CABG, coronary artery bypass graft; ISR, in-stent restenosis; BMS, bare-metal stents; DES, drug-eluting stents; ST, stent thrombosis; ncRNA, Non-coding RNA; PDGF-Rα, PDGF receptor α; KLF4, Kruppel-like factor 4; ELK-1, ELK1, member of ETS oncogene family; MECP2, methylCpG binding protein 2; HDAC4, histone deacetylase 4; EVI1, ecotropic virus integration site 1 Protein Homolog; uPA, urokinase-type plasminogen activator; SMAD3, SMAD family member 3; FoxO4, forkhead box O4; PDGF-BB, platelet-derived growth factor-BB; oxLDL, oxidized low-density lipoprotein; FGF1, fibroblast growth factor 1; MLC9, myosin light chain 9; PTEN, Phosphatase and Tensin Homolog; LATS2, large tumor suppressor homolog 2; CREG, cellular repressor of E1A-stimulated genes; AngII, angiotensin II; HA, Hyaluronan; Dlk1, Delta-like 1 homolog; ITGA5, integrin-α5; ICAM-1, intracellular adhesion molecule 1; STAT5A, signal transducer and activator of transcription 5A; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor-2; FGFR1, fibroblast growth factor receptor-1; NO, nitric oxide; LEENE, lncRNA enhancing eNOS expression; HOTAIR, HOX Antisense Intergenic RNA; circRNA, circularRNA; MIAT, myocardial infarction associated transcript; ceRNA, competing endogenous RNA; RNA-RNCR3, retinal non-coding RNA 3; GAS5, growth-arrest specific transcript 5

* Corresponding author at: Division of Cardiology, University Magna Graecia, Catanzaro, Italy.
E-mail address: Indolfi@unicz.it (C. Indolfi).

https://doi.org/10.1016/j.vph.2018.10.006
Received 10 March 2018; Received in revised form 8 October 2018; Accepted 18 October 2018
Available online 24 October 2018

2. The role of noncoding RNAs

Recently, it became evident that only around 2% of the entire human genome is responsible for protein production. Non-coding RNA (ncRNA) is transcribed from the remaining so-called "noncoding" genome regions. ncRNA is a heterogeneous class of molecules. Among these, miRNAs - short nucleotides that are able to modulate the expression of a large number of genes, including those involved in vascular remodeling - have been extensively studied [5,12–16]. miRNAs have also been proposed as biomarkers for different cardiovascular diseases [17–20]. More recently, long noncoding RNAs (lncRNAs) have raised interest for their biological functions. LncRNAs are a large and heterogeneous class of different RNA molecules. They are transcribed by the RNA polymerase II (RNA Pol II) and are usually longer than 200 nucleotides. Given their complexity and heterogeneity in structure and function, many different classifications of lncRNAs have been proposed. For example, lncRNAs could be classified in the following four subtypes according to their molecular mechanism: decoy, signal, guide, and scaffold lncRNAs [21]. On the basis of their genomic location, lncRNAs can be classified into: i) intergenic (transcribed from the genomic sequences located between genes); ii) intronic (transcribed from intronic regions); iii) sense (transcribed from sense strand of protein-coding genes); iv) antisense (transcribed from the antisense strand of protein-coding genes); and v) bidirectional (transcribed in the opposite direction to protein-coding genes) [13]. In addition, lncRNAs can be classified into different subtypes based on cellular localization and/or their functionality as cis and/or trans acting regulators [22]. Although the function of most lncRNAs remains unknown, evidence is emerging that these molecules play critical roles in several biological processes. Indeed, lncRNAs contribute to various aspects of gene regulation, such as chromatin remodeling and interactions, RNA transcription, alternative splicing, and RNA processing [12,23,24]. Given their established ability to interact with DNA, RNAs and proteins targets, it has become evident that lncRNAs might function as decoys [25], scaffolds [26], signals [27], sponges [28], and enhancer RNAs [29]. LncRNAs play a key role in various cellular events including proliferation, migration, apoptosis, differentiation and development [30–32]. The function of lncRNAs is determined by their structure, expression and subcellular distribution [33]. In the cytoplasm, these transcripts interact with RNA and protein influencing miRNA function [34], mRNA stability and their translation [35]. In the nucleus, lncRNAs can influence epigenetic control of transcription by interactions with chromatin-modifying proteins [36]. Nuclear lncRNAs can also regulate transcription by enhancer-like activity or by influencing alternative splicing of pre-mRNAs [37]. Despite their functional complexity and relatively poor conservation, lncRNAs have attracted large interest because of their therapeutic potential. To date, several studies have shown that alterations of lncRNAs function and expression can lead to a variety of pathological human processes, including cardiovascular diseases. These molecules have been studied also as potential biomarkers and therapeutic targets in human disorders such as atherosclerosis [38–40], heart failure [41–43] and CAD [44,45]. Here, we overview the role of miRNAs and lncRNAs in the molecular mechanisms underlying vascular remodeling with a focus on their function in cells of the vascular wall. Despite the exact mechanisms have not been fully elucidated for all molecules yet, an increasing number of studies conducted to identify these lncRNAs and their role is coming up. Details on known biological mechanisms and/or specific targets are in Tables 1 and 2.

3. NcRNAs in restenosis

In recent years, dysregulation of ncRNAs has been found in a variety of vascular obstructive diseases, including restenosis after stent implantation. In particular, several ncRNAs were shown to modulate the phenotypic switch of VSMCs. VSMCs are highly specialized cells characterized by an extraordinary plasticity in adult animals in response to a wide range of stimuli [46]. During vascular remodeling, VSMCs undergo a phenotype switch from a contractile to a proliferative status [47,48]. This results in the accumulation of dedifferentiated VSMCs in the intima and is central to a number of vascular pathologies such as arteriosclerosis, restenosis, or diabetes mellitus [20,49,50]. For this reason, it is important to understand the mechanisms that govern VSMCs phenotype.

In this context, several miRNAs have been recognized as modulators of the phenotype switch of VSMCs. In addition, more recently lncRNAs have emerged as important regulators for VSMC phenotype. The next paragraph describes the biological functions of miRNAs and lncRNAs and discusses their involvement in vascular response to injury. Representative examples of ncRNAs involved in VSMC phenotypic switch are shown in Fig. 1.

4. miRNA in VSMC phenotypic change related to vascular proliferative diseases

4.1. miR-143/145 cluster

A large number of miRNAs have been identified as important post-transcriptional regulators of gene expression in several diseases. Among them, miR-143 and miR-145 have been identified as master regulators of VSMC phenotypic switch during vascular development [51] and in vascular diseases [5,52]. Elia L. et al. showed that the genomic ablation of miR-145 and miR-143 results in an incomplete differentiation of VSMC in mice [52]. In line with these results, miR-143 and miR-145 were downregulated in proliferating VSMCs *in vitro* and in experimental mice model. In fact, overexpression of miR-145 affected VSMC proliferation and the formation of neointimal lesions in injured rat carotid arteries [53]. The involvement of miR-143 and miR-145 in the molecular mechanisms underlying neointimal hyperplasia was also confirmed in a mouse model of vascular injury [52]. Altogether, multiple studies revealed that the regulation of multiple target genes by miR-145/miR-143 is essential for maintenance of the contractile phenotype in VSMCs. For example, miR-145 positively regulates VSMC differentiation markers by suppressing the Kruppel-like factor 5 (KLF-5) [53], resulting in a significant reduction of cell proliferation and migration. Quintavalle and colleagues demonstrated the role of miR-145 and miR-143 in the control of VSMC podosome formation [54]. In their study, PKC-ε, the PDGF receptor α (PDGF-Rα) and an actin-bundling protein (Fascin) were found to be direct targets of miR-145 and miR-143. Furthermore, Cordes et al. reported KLF4 (Kruppel-like factor 4) and ELK-1 (ELK1, member of ETS oncogene family) as target genes of miR-145 and miR-143, respectively [51]. Finally, the modulation of these transcription factors contributes to the fate of VSMCs. The strong involvement of miR-143/miR-145 in the molecular mechanisms underlying neointima formation is further emphasized by the clinical evidence that circulating levels of miR-143 are able to predict in-stent restenosis in patients with peripheral arterial occlusive disease [55] or CAD [56].

4.2. miR-22

In addition to miR-145 and miR-143, miR-22 is known to play a key role in VSMC differentiation [57]. In a recent study Yang F. et al. showed that miR-22 is downregulated in injured femoral arteries, where it targets the 3′UTR of methylCpG binding protein 2 (MECP2), histone deacetylase 4 (HDAC4) and ecotropic virus integration site 1 Protein Homolog (EVI1). Using *in vivo* gain- or loss-of-function experiments, the authors demonstrated that over-expression of miR-22 decreases VSMC proliferation, and inhibits neointima formation in wire-injured femoral arteries, whereas the opposite effect was obtained with the inhibition of miR-22 [58].

Table 1
Noncoding RNAs in vascular smooth muscle cells.

lncRNA	Mechanisms/target	Biological significance	Ref.
miR-145/143	KLF4, KLF5, Elk-1	Proliferation; Differentiation markers	[51–56]
miR-22	MECP2, HDAC4, EVI1	Proliferation	[57,58]
miR-133	Sp1 and Moesin	Proliferation; Migration, Differentiation markers	[46,59]
miR-23b	FOXO4, Smad3, uPA	Proliferation; Migration	[60]
miR-125a-5p	ETS-1, PDGF-BB signaling	Proliferation; Migration	[61]
miR-26a	Smad1, PDGF-BB signaling	Proliferation	[77]
miR-612	Akt2, PDGF-BB signaling	Proliferation; Migration	[78]
miR-195	Cdc42, cyclin D1, FGF1	Proliferation; Migration; Inflammation	[62]
miR-663	JUNB; MLC9	Migration, Differentiation markers	[63]
miR-9	PDGFR	Proliferation	[65]
miR-599	TGF- β2	Proliferation, Migration	[66]
miR-21	PTEN	Proliferation	[67–69]
miR-221/miR222	p27(Kip1); p57(Kip2)	Proliferation	[71]
miR-146	KLF4	Proliferation	[72]
miR-206	ZFP580	Proliferation, Differentiation markers	[73]
miR-181b	Activation of MAPK and PI3K signaling	Proliferation, Migration	[74]
miR-31	LATS2, CREG	Proliferation	[76]
Lnc-Ang362 (I)	Host transcript for miR-221 and miR-222	Proliferation	[81]
H19 (I)	RNA sponge for Let-7 family	Unknown	[85,87,88]
ANRIL (O; D; F)	Regulatory role of CDKN2A/B expression	Proliferation	[84,89]
lincRNA-p21 (I)	Component of the p53 pathway	Proliferation, apoptosis	[39]
HAS2-AS1 (O, C)	HAS2 transcription regulation	Unknown	[90]
SMILR (I)	Response to PDGF and IL-1α	Proliferation	[93]
SENCR (O, B)	Negative regulation of MDK and PTN	Migration, contrattily	[90,94,95]
HIF1α-AS1 (O)	Regulatory role of apoptosis pathway	Apoptosis	[199]
GAS5 (I)	Direct interaction with ANXA2	Proliferation, migration	[97]
MEG3 (C)	Role in p53 and MMP-2 expression	Proliferation, migration, apoptosis	[99–101]
MYOSLID (Q)	Role in nuclear translocation of MKL	Proliferation, contractile phenotype	[102]
RNCR3 (I, F)	Response to ox-LDL	Proliferation, migration, apoptosis, atheroprotective	[40]
MALAT1 (B, I)	Unknown	Proliferation, migration	[104]
AK098656 (D).	Unknown.	Proliferation, migration, differentiation markers.	[105]

Classification of lncRNAs by Mechanism of Action: **Signal lncRNAs (A)**; **decoy lncRNAs (B)**; **guide lncRNAs (C)**; **scaffold lncRNAs (D)**; **enhancer lncRNAs (E)**; **sponge lncRNAs (F)**.
Classification of lncRNAs based on their effects on DNA sequences: **Cis-regulatory lncRNAs (G)**; **trans-regulatory lncRNAs (H)**.
Classification of lncRNAs based on their genomic location: **Intergenic lncRNAs (I)**; **intronic lncRNAs (L)**; **bidirectional lncRNAs (M)**; **sense lncRNAs (N)**; **antisense lncRNAs (O)**.
Classification according to lncRNA subcellular localization: **Nuclear lncRNAs (P)**; **cytosolic lncRNAs (Q)**.
Abbreviations: KLF4: Kruppel-like factor 4; KLF5: Kruppel-like factor 5; Elk-1: ETS domain-containing protein; HDAC4: Histone Deacetylase 4; FOXO4: Forkhead box protein O4; uPA: urokinase-type plasminogen activator; PDGF: Platelet-derived growth factor; FGF: fibroblast growth factor; TGF: Transforming growth factor; PTEN: Phosphatase and tensin homolog; ZFP5: Zinc finger protein 5; MAPK: mitogen-activated protein kinase; PI3K: Phosphoinositide 3-kinase; LTSK2: Large Tumor Suppressor Kinase 2; CREG: cellular repressor of E1A-stimulated genes; CDKN2: cyclin-dependent kinase Inhibitor 2; HAS2: Hyaluronan synthase 2; MDK: Midkine; PTN: Pleiotrophin; ANXA2: Annexin A2; MMP-2: Matrix metalloproteinases 2; MKL: megakaryoblastic leukemia 1.

4.3. miR-133

Using a rat model, we observed a reduction in miR-133 levels in balloon-injured carotid artery compared to the control [46]. On the basis of both *in vitro* and *in vivo* data, our group found that miR-133 is implicated in the control of vascular cell proliferation and migration. In addition, adenovirus-mediated overexpression of miR-133 attenuates neointimal formation following balloon injury whereas repression of its endogenous levels induces the opposite effects. Of note, miR-133 reduced the proliferation and migration of VSMCs by targeting the transcription factor Sp-1 and Moesin. In line with these experimental findings, an increased transcoronary concentration gradient of miR-133a predicts a higher rate of target lesion revascularization because of in-stent restenosis [59].

4.4. miR-23b

Similarly, we showed that miR-23b modulates the VSMCs phenotypic switch [60]. Indeed, miR-23b inhibits the proliferation and migration of VSMCs through the direct regulation of uPA (urokinase-type plasminogen activator), SMAD3 (SMAD family member 3), and FoxO4 (forkhead box O4). According to these data, we found that injury-induced neointimal formation is significantly reduced by miR-23b overexpression (Fig. 2).

4.5. miR-125a-5p

Our group also investigated the function of miR-125a-5p, demonstrating that it is down-regulated in proliferating VSMCs. Finally and foremost, miR-125a-5p negatively regulates cell migration and growth in response to platelet-derived growth factor-BB (PDGF-BB) [61].

4.6. miR-195

Other important miRNAs regulating VSMCs biology and vascular restenosis include miR-195 and miR-663 [62,63]. miR-195 was shown to be reduced by oxidized low-density lipoprotein (oxLDL) and to limit VSMCs proliferation, migration and the expression of pro-inflammatory biomarkers, through targeting of Cdc42, cyclin D1, and FGF1 (fibroblast growth factor 1). In addition, miR-195 overexpression was able to inhibit intimal thickening in rat carotid artery after vascular injury [62]. Of note, circulating levels of miR-195 have been found to be independent predictors of target vessel revascularization 2 years after stenting in patients with peripheral artery disease [64].

4.7. miR-663

miR-663 was reported to negatively regulate VSMCs migration and the expression of differentiation marker genes in humans by targeting

Table 2
Noncoding RNAs in endothelial cells.

lncRNA	Mechanisms/target	Biological significance	Ref.
miR-126	SPRED-1, PIK3R, VCAM-1, Dlk1, ALCAM, setD5, NF-kB, VEGF and TNF-α signaling	Angiogenesis, Inflammation	[108–115]
miR-17/92a	KLF-2, KLF-4, ITGA5, eNOS modulation	Angiogenesis, Atherosclerosis	[116–120,122]
miR-221/222	eNOS modulation, c-kit, ICAM-1, ETS-1, STAT5A	Proliferation, Migration, Angiogenesis, Atherosclerosis	[125–128,133–135]
miR-21	PTEN, SMAD7, type I and type V collagen, proteoglycan, eNOS modulation, PPAR-α, NOX4	Angiogenesis, Inflammation, shear stress response, hypertension	[137–142]
miR-16	RhoGDIα, VEGF, VEGFR2, FGFR1	Proliferation, Migration, Atherosclerosis	[143–146]
NOS3AS/ATG9B (O)	eNOS modulation	Unknown	[147,149]
HIF-1AS (O)	eNOS modulation	Proliferation, Apoptosis Atherosclerosis	[151,152]
LEENE (C)	Recruitment of RNA pol II, eNOS modulation	Unknown	[154]
MANTIS (H, D)	Scaffold Chromatin-Remodeling Complex,	Transcription, Angiogenesis	[155]
HOTAIR (O, A, B, C, H)	Scaffold for protein complex, VEGF signling thorugh PI3K/AKT-IRF1	Histone modification, protein ubiquitination, Angiogenesis	[157–162]
CZNF292 (Q)	circRNA, splicing modulation	Angiogenesis, Sprouting	[164]
MALAT1 (B, I)	ceRNA	Angiogenesis	[163–170]
MEG3 (C)	Notch signaling, p53/NOX4	Angiogenesis	[99,163,173,174]
MIAT (B, I)	ceRNA (miR-150-5p)	Angiogenesis	[175–177]
MKI67IP-3 (F)	ceRNA (let-7e)	Inflammation	[178]
RNA-RNCR3 (I, F)	ceRNA (miR-185-5p)	Atheroprotective	[40,180]
TIE1-AS (O)	Negative regulation of Tie1	Angiogenesis	[181]
TERMINATOR (I)	Unknown	Endothelial cells differentiation	[182]
ALIEN (I)	Unknown	Vascular development	[182]
PUNISHER (O)	Unknown	Proliferation, adhesion	[182]
DLL4-AS (O)	Unknown	Proliferation, Migration	[184]
SENCR (O, B)	CCL5, CEACAM1, CX3CL1	Angiogenesis	[87,184]
ANRIL (O, D, F)	Unknown	Inflammation, cell cycle	[38,84,185–189]
GAS5 (I)	β-catenin signaling pathway	Apoptosis	[190–194]

Classification of lncRNAs by Mechanism of Action: **Signal lncRNAs (A)**; **decoy lncRNAs (B)**; **guide lncRNAs (C)**; **scaffold lncRNAs (D)**; **enhancer lncRNAs (E)**; **sponge lncRNAs (F)**.
Classification of lncRNAs based on their effects on DNA sequences: **Cis-regulatory lncRNAs (G)**; **trans-regulatory lncRNAs (H)**.
Classification of lncRNAs based on their genomic location: **Intergenic lncRNAs (I)**; **intronic lncRNAs (L)**; **bidirectional lncRNAs (M)**; **sense lncRNAs (N)**; **antisense lncRNAs (O)**.
Classification according to lncRNA subcellular localization: **Nuclear lncRNAs (P)**; **cytosolic lncRNAs (Q)**.
Abbreviations: SPRED-1: Sprouty-related, EVH1 domain-containing protein 1; PIK3R: Phosphoinositide 3-kinase receptor; VCAM-1: Vascular cell adhesion protein 1; Dlk1: Delta Like Non-Canonical Notch Ligand 1; ALCAM: activated leukocyte cell adhesion molecule; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; VEGF: Vascular endothelial growth factor; TNF-α: Tumor necrosis factor; KLF-2: Kruppel-like factor 2; KLF-4: Kruppel-like factor 4; ITGA5: Integrin Subunit Alpha 5; ICAM-1: Intercellular Adhesion Molecule 1; STAT5A: Signal Transducer And Activator Of Transcription 5A; PTEN: Phosphatase and tensin homolog; PPAR-α: Peroxisome proliferator-activated receptor alpha; NOX4: NADPH oxidase 4; RhoGDIα: Rho GDP-dissociation inhibitor 1; VEGFR2: Vascular endothelial growth factor receptor 2; FGFR1: fibroblast growth factor receptor 1; eNOS: nitric oxide synthase 3; PRC2: polycomb repressive complex 2; LSD1: Lysine-specific histone demethylase 1A; ceRNA: competing endogenous RNAs; CCL5: Chemokine (C—C motif) ligand 5; CEACAM1: Carcinoembryonic Antigen Related Cell Adhesion Molecule 1; CX3CL1: C-X3-C Motif Chemokine Ligand 1.

JUNB and myosin light chain 9 (MLC9). Furthermore, the overexpression of miR-663 *in vivo* reduced neointimal lesion formation after vascular injury induced by carotid artery ligation in mice [63]. Further examples of miRNA-mediated repression of vascular proliferative diseases include miR-9 [65] and miR-599 [66].

4.8. miR-21

Intriguing experiments by Ji R. et al. showed that miR-21 promotes VSMCs proliferation by directly targeting Phosphatase and Tensin Homolog (PTEN), a critical regulator of VSMCs function both *in vivo* and *in vitro* [67]. In line with this hypothesis, the delivery of antisense oligonucleotides against miR-21 to the injured artery inhibited neointima formation in rats [67]. The importance of miR-21 in modulating the vascular response to injury is further supported by studies in animal models of in-stent restenosis. In particular, McDonald RA. et al. showed that the genomic ablation of miR-21 reduced vascular inflammation and remodeling after vascular stenting in mice [68]. Wang et al. also tested the effects of local delivery of miR-21 inhibitors on injured artery, using anti-miR-21–coated stents, they demonstrated that this approach is able to significantly attenuate in-stent restenosis without affecting re-endothelialization [69]. He et al. reported significantly higher circulating levels of miR-21 in patients with angiographic evidence of in-stent restenosis compared to controls [56], supporting the concept that the modulation of miR-21 is also clinically relevant in humans.

4.9. miR-221/222

Other examples of up-regulated miRNAs in vascular restenosis include miR-221 and miR-222 [70]. Both miRNAs are able to promote VSMCs proliferation. This is accomplished, at least in part, by suppressing the target genes p27 (Kip1) and p57 (Kip2). The knockdown of miR-221 and miR-222 attenuated the neointimal hyperplasia in rat carotid artery after angioplasty [70]. A recent report also reported increased miR-221 and miR-222 levels in VSMCs and arteries of diabetic mice. Interestingly, the inhibition of these two miRNAs prevented the abnormal VSMCs proliferation in response to arterial injury in diabetes mellitus [71].

4.10. miR-146a

miR-146a is a positive regulator of the synthetic phenotype of VSMCs *in vitro* and *in vivo* by targeting KLF4 [72]. MiR-146a overexpression has been shown to increase VSMCs proliferation, whereas its inhibition in injured rat carotid arteries decreased neointimal hyperplasia.

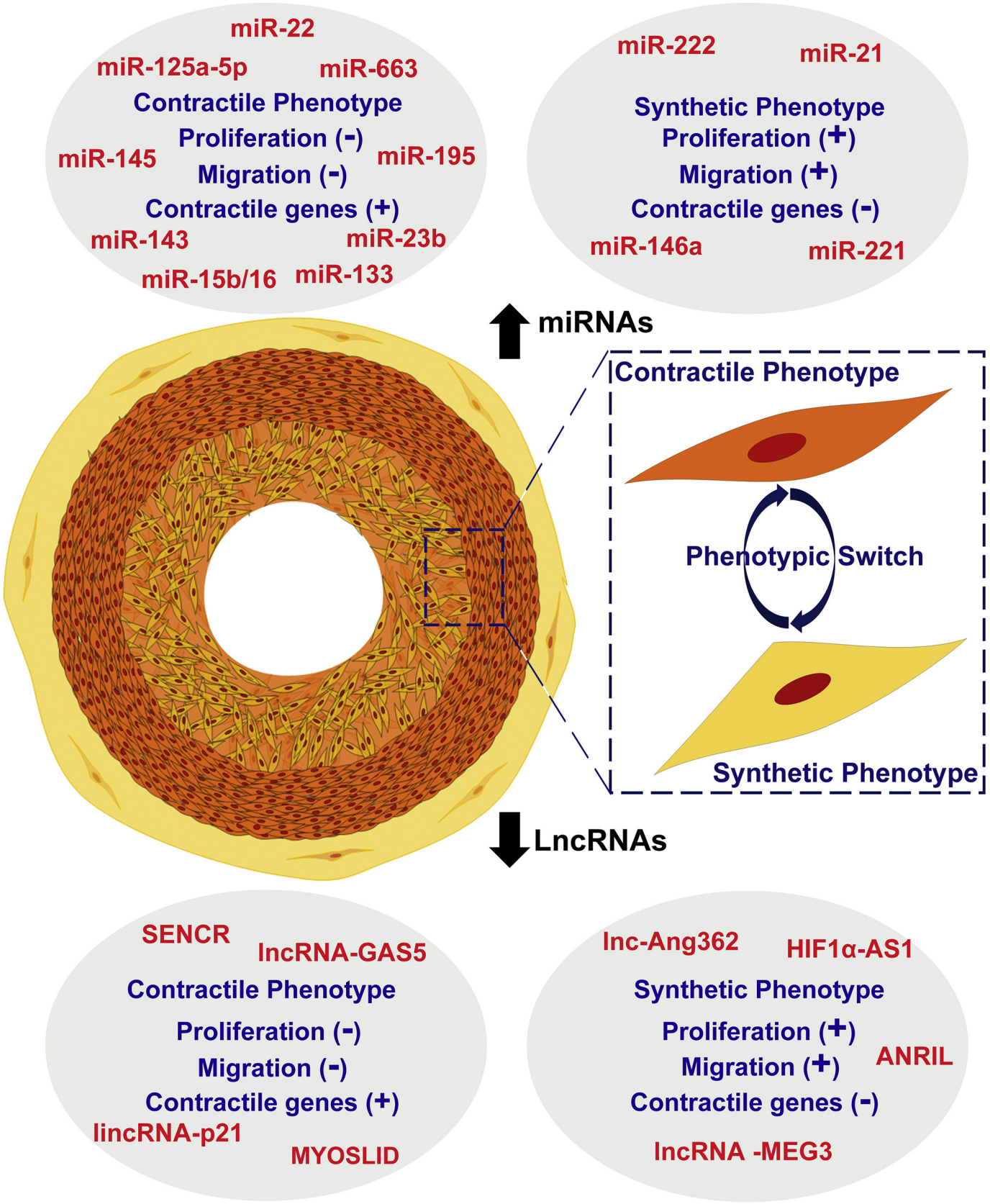

Fig. 1. Involvement of miRNAs and lncRNAs in the modulation of VSMCs phenotypic switch. Graphical representation of VSMC phenotypic switching in vascular proliferative disease. Examples of miRNAs and lncRNA reported to regulate the VSMC phenotype are shown. **SENCR** indicates Smooth muscle and Endothelial cell-enriched migration/differentiation-associated long NonCoding RNA; **lncRNA-GAS5**, growth arrest specific transcript 5; **MYOSLID**, myocardin-induced Smooth muscle LncRNA, Inducer of Differentiation; **lincRNA-p21**, long intergenic non-coding RNA p21; **ANRIL**, anti-sense RNA in the INK4 locus; **HIF1α-AS1**, long non-coding RNA hypoxia-inducible factor 1α-antisense 1;**lncRNA -MEG3**, long non-coding RNA maternally expressed gene 3.

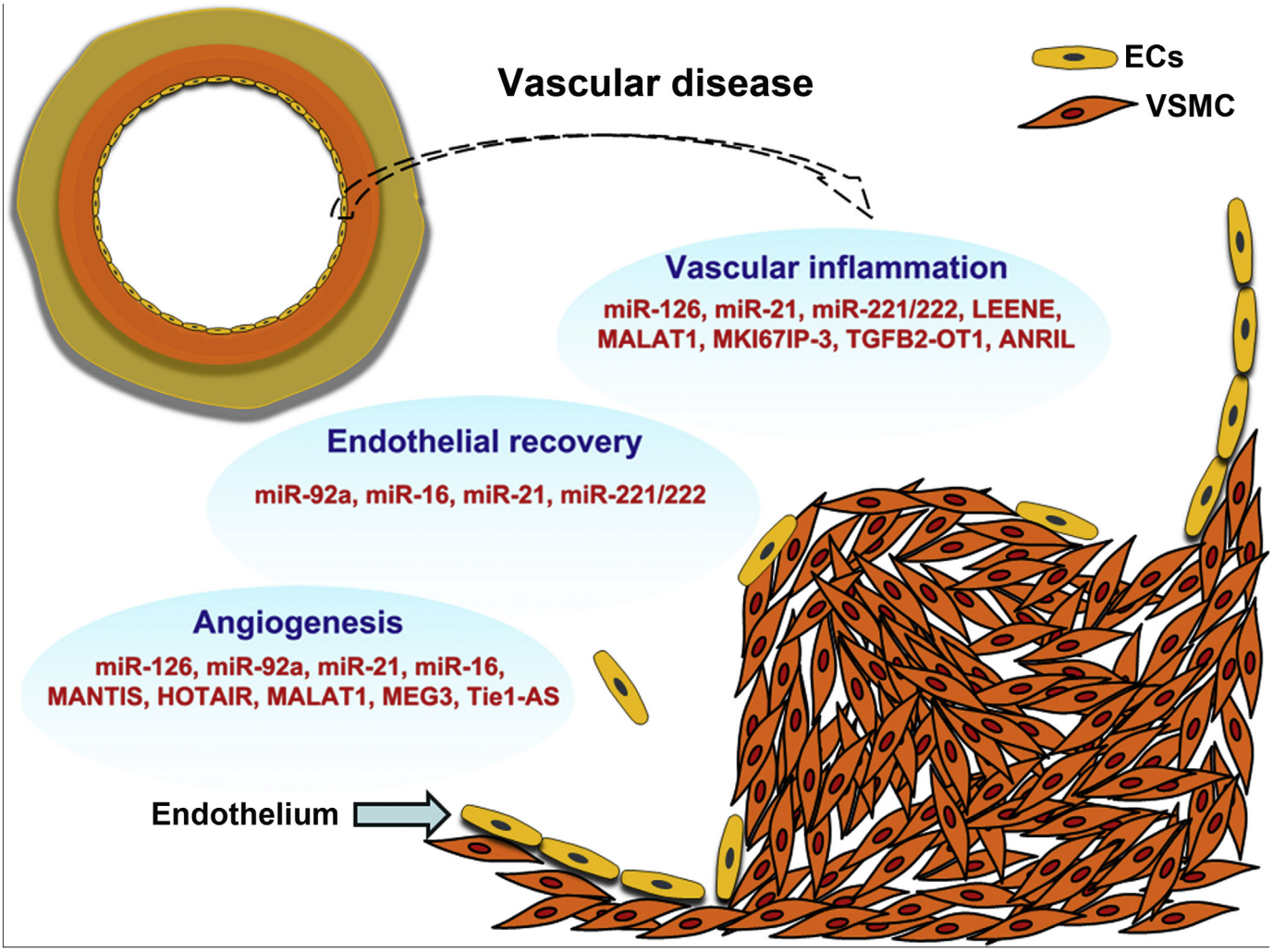

Fig. 2. Involvement of miRNAs and lncRNAs in vascular biology. Graphical representation of illustrative examples of miRNA and lncRNA involved in angiogenesis, inflammatory response and endothelial recovery (see text and Table 2 for details on specific mechanism of all displayed ncRNAs). **MANTIS** indicates lncRNA n342419; **HOTAIR**, HOX transcript antisense RNA; **MALAT1**, metastasis-associated lung adenocarcinoma transcript-1; **MEG3**, maternally expressed 3; **Tie1-AS**, tyrosine kinase containing immunoglobulin and epidermal growth factor homology domain-1 antisense; **MKI67IP-3**, long intergenic non-protein coding RNA 1826; **TGFB2-OT1**, TGFB2 overlapping transcript 1; **ANRIL**, antisense noncoding RNA in the INK4 locus.

4.11. miR-206

Sun H et al. evaluated the role of miR-206 in the phenotypic switch of VSMCs, and showed that its expression was significantly increased in proliferating VSMCs of injured vascular walls. On the contrary, lentivirus-mediated inhibition of miR-206 reduced neointimal formation following balloon injury [73].

4.12. miR-181b

miR-181b promotes the proliferation and migration of VSMCs through the activation of PI3K and MAPK signaling pathways. In line with this hypothesis, the inhibition of endogenous miR-181b decreased neointima hyperplasia in rat carotid arteries after angioplasty [74].

4.13. miR-31

According to a recent report, the expression levels of miR-31 are significantly increased in injured rat carotid arteries [75]. miR-31 promotes VSMCs proliferation through the downregulation of large tumor suppressor homolog 2 (LATS2), which is known to inhibit cell growth by several mechanisms. Additionally, miR-31 downregulates the cellular repressor of E1A-stimulated genes (CREG) level to promote synthetic phenotype of human VSMCs [76].

4.14. Other upcoming miRs

Recent studies indicated that additional miRNAs are involved in the PDGF signaling. For example, Yang et al. identified miR-26a as a positive regulator of PDGF-BB-mediated VSMCs phenotypic transition by targeting Smad1 [77], while Chen C. et al. showed that miR-612 suppressed the PDGF-BB-induced proliferation and migration of VSMCs [78]. Mechanistically, the authors demonstrated that miR-612 directly targets AKT2 to block cell cycle progression from G1 to the S phase. Although these results reveal a potential role for miR-125a-5p, miR-612 and miR-26a in the phenotypic switch of VSMCs in response to the PDGF signaling, the effects of the these miRNAs in vascular restenosis remain to be confirmed in the clinical setting and further studies in animal models of vascular injury assessing the impact of their modulation are still needed. Moreover, miR-15b and miR-16 were shown to promote the VSMC contractile phenotype *in vitro* and *in vivo* [79]. Both miRNAs influence VSMC proliferation and migration by directly targeting Yes-Associated Protein (YAP), a known positive modulator of cell cycle progression [80]. Adenovirus-mediated concomitant

overexpression of miR-15b and miR-16 decreased neointima formation in injured rat carotid arteries, suggesting that modulation of these miRNAs may have therapeutic potential for the treatment of proliferative vascular diseases.

MiRNA involved in the modulation of VSMC phenotype are listed in Table 1.

5. LncRNAs in vascular smooth muscle cells

In recent years, a number of new classes of noncoding RNAs have been studied (Table 1), although this field has been relatively underexplored [12,13].

5.1. Lnc-Ang362

One of the first studies described the involvement of lncRNA in mediating Ang II signaling in rat VSMCs [81]. The authors found that the treatment with Angiotensin II is responsible for significant expression change of 29 lncRNAs. They focused on the role of *Lnc-Ang362*, which is located in proximity to miR-221 and miR-222, which are involved in VSMCs proliferation and the development of neointimal lesions [82]. They hypothesized that *Lnc-Ang362* is upregulated in response to angiotensin II (AngII), in line with what observed with the two co-localized miRNAs. Indeed, *lnc-Ang362* acts as host transcript for miR-221 and miR-222, and its dowregulation causes a reduced miR221/222 expression, and subsequently affects VSMC phenotype.

Since then, several studies have been performed to investigate the role of lncRNAs in human VSMCs. Early works focused on the role of previously identified *lncRNAs H19* [83] and *ANRIL* [84], on human VSMCs function.

5.2. H19

The *H19* gene is a well-known gene involved in cell differentiation and growth processes. Its RNA transcript is also the precursor of miR-675. Independent studies indicated that *H19* controls the expression of miR-675 to regulate placenta growth [85]. The precise function of *H19* in pathological VSMCs is still partly known, but recent studies suggested that *H19* lncRNA functions as a sponge of the let-7 family, that is known to protect VSMCs from oxidative stress [86,87]. More recently, Lv et al. demonstrated that the co-transcribed miR-675 aggravates restenosis in rat carotid artery balloon injury model by targeting PTEN [88].

5.3. ANRIL

The lncRNA *ANRIL* is located in the 9p21.3 region. This locus has been associated with genetic susceptibility for intracranial aneurysms, coronary diseases, and type II diabetes in many studies [89]. Further studies showed that *ANRIL* regulated VSMCs proliferation through CDKN2A/B. The knocking-down of *ANRIL* in VSMCs inhibited cell proliferation and augmented the expression of CDKN2B [84], suggesting a potential mechanism by which this genetic locus is related to diseases characterized by alterations of vascular formation or remodeling [89].

5.4. lncRNA-p21

The *lncRNA-p21* is downregulated in atherosclerotic lesions. Experimental studies showed that this lncRNA represses VSMCs proliferation while its downregulation exacerbates restenosis following acute injury [39]. Indeed, knocking-down of *lncRNA-p21* suppresses p53 activity and changes the balance between MDM2/p53 and p300/p53 complexes. Finally, clinical studies revealed that coronary tissues from patients with CAD exhibit reduced levels of lncRNA-p21 compared to aorta tissues from patients without CAD [39].

5.5. HAS1/2-AS1

Recently, Vigetti et al. observed that the expression of *HAS2-AS1* in human plaques correlates directly with lesion severity [90]. HAS2 is fundamental for Hyaluronan (HA) synthesis, whereas previous studies have demonstrated that HA vascular deposition is implicated in vessel wall thickening, extracellular matrix remodeling, and neointima formation [91,92]. Interestingly, Vigetti et al. demonstrated that *HAS1-AS1* enrichment was required for HAS2 upregulation in human aortic VSMCs upon O-GlcNAcylation, but not through an increase of mRNA stability as previously identified in other cell types.

5.6. SMILR

Using VSMCs isolated from saphenous veins of human donors and stimulated *in vitro* with interleukin 1-alpha and PDGF, authors from the Glasgow University recently identified a novel lncRNA, which they named smooth muscle-induced lncRNA enhances replication (*SMILR*). Increased *SMILR* levels were observed by the authors in human unstable atherosclerotic plaques and in plasma from patients with atherosclerosis and ongoing inflammation, evaluated as increased hs-CRP levels [93]. These findings are particularly relevant on the clinical level, as SMILR plays a role in promoting VSMCs proliferation and restenosis. In fact, the knockdown of *SMILR* resulted in a significant reduction of cell proliferation [93].

5.7. SENCR

Lately, the Miano Lab reported a lncRNA expressed in both VSMCs and ECs [94]. They screened human coronary artery SMCs and identified a novel lncRNA, which they called *SENCR* that is an antisense to the EC-restricted *Fli1* gene. *SENCR* knockdown in VSMCs led to a downregulation of VSMC differentiation markers and an increase in two pro-migratory genes, MDK and PTN. This study demonstrated that *SENCR* is involved in maintaining a contractile phenotype, thereby uncovering a novel lncRNA-mediated mechanism in regulating VSMC phenotype. An animal study demonstrated that down-regulation of a specific lncRNA within Fli1 gene that the authors suggest to be the mouse orthologue of human *SENCR* promotes VSMCs proliferation and migration in db/db mice [95]. According to the result of luciferase assays, it was shown that *Sencr* knockdown enhanced the expression of FoxO1 and TRPC6 in VSMCs [95]. However, direct proof of that the lncRNA within Fli1 gene found in mouse is the ortholog of human *SENCR* awaits further investiagtion.

5.8. HIF1α-AS1

In patients with aorta aneurysms, Zhao et al. found that knockdown of *HIF1α-AS1* in VSMCs, resulting in the inhibition of apoptosis and lower levels of apoptosis-related proteins [96].

5.9. GAS5

Li et al. screened lncRNAs in varicose veins and found that *lncRNA-GAS5* (growth-arrest specific transcript 5) inhibited the proliferation and migration of VSMCs. Mechanistically, they found that *GAS5* interacts with ANXA2. Indeed, they observed that the inhibition of ANXA2 through *GAS5* rescued the proliferative phenotype, suggesting that ANXA2 is a key target of *GAS5* in the modulation of VSMCs [97]. Moreover, Tang et al. [98] demonstrated that *Gas5* suppresses TGF-β/Smad3 signaling during VSMC differentiation. They found that forced expression of *Gas5* or its knowkdown, respectively blocked inhibited or increased the expression of VSMC contractile proteins.

5.10. MEG3

The lncRNA *MEG3* was recently annotated and found to be implicated in vascular diseases. Indeed, a recent study showed that *MEG3* regulates endothelial aging while mediating angiogenesis [99]. *MEG3* is under the control of IFN-γ, affecting VSMCs survival and migration during uterovascular transformation [100]. More recently, Sun Z et al. demonstrated that *MEG3* knockdown affects the proliferation and migration of VSMCs of pulmonary arteries, regulating cell cycle progression [101].

5.11. MYOSLID

The lncRNA *MYOSLID* has been shown to promote VSMC phenotypic switching while reducing VSMCs proliferation [102]. It is a direct target of MYOCD/SRF and TGFβ/SMAD pathways. Inhibition of *MYOSLID* in VSMCs blocks the nuclear translocation of MKL, disrupting actin stress fiber formation. On the other hand, the loss of *MYOSLID* abrogates TGFβ1-induced SMAD2 phosphorylation [102]. Consistent with this latter finding, *MYOSLID* levels were found to be significantly lower in failed arteriovenous fistulas (AVF) [102]. Interestingly, along with reduced *MYOSLID* levels, also MYOCD but not SRF mRNA levels were downregulated, which fits previous evidence of reduced MYOCD levels in vascular disease [103].

5.12. RNCR3

Recently, Shan K et al. [40] showed that *lncRNA-RNCR3* retinal noncoding RNA 3 (RNA-RNCR3) is upregulated in mouse and human aortic atherosclerotic lesions, and cultured ECs and VSMCs upon ox-LDL treatment *in vitro*. *RNCR3* knockdown decreases EC and VSMC proliferation *in vivo*, and reduces proliferation, migration, and accelerates apoptosis development of EC and VSMC *in vitro*. This study reveals that *RNCR3* has an atheroprotective role, and could be useful for the treatment of atherosclerosis-related vascular diseases.

5.13. MALAT1

Yu CK et al. [104] studied the role of *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1) in stiffness-sensitive (SS) transcriptome of human aortic and coronary VSMCs. They found that *MALAT1* regulates stiffness-dependent VSMC proliferation and migration both *in vitro* and *in vivo*. These data suggest that SS lncRNAs can act as regulators of stiffness-related phenotypes.

5.14. AK098656

A recent study by Jin L et al. [105] demonstrated that *AK098656*, a novel vascular smooth muscle cell-dominant lncRNA, promotes hypertension. *LncRNA-AK098656* is strongly upregulated in the plasma of hypertensive patients, and predominantly expressed in VSMCs. *AK098656* promoted the synthetic phenotype of VSMCs, increasing VSMC proliferation and migration, upregulating extracellular matrix proteins, and lowering contractile protein levels. *In vivo*, *AK098656* transgenic rats showed spontaneous development of hypertension, with elevated VSMCs synthetic phenotype, narrowed resistant arteries and hypertrophy.

Altogether, a growing body of evidence demonstrates that lncRNAs play a key role in the regulation of proliferation, migration and matrix synthesis capability of VSMCs, key biological mechanisms underlying vascular remodeling and its clinical effects, such as formation and progression of atherosclerotic lesions or restenosis after PCI. These results highlight new promising therapeutic targets that could be exploited to interfere with adverse vascular remodeling processes.

6. ncRNAs in endothelial pathophysiology

Endothelial function is crucial for the maintenance of vascular physiology and to promote long-term success of stent implantation. ECs modulate the vessel response to variations in shear stress, and a quick regeneration of the luminal ECs monolayer after stenting is pivotal to prevent side effects such as restenosis and intra-stent thrombosis [5,12,106]. On the contrary, ECs injury is a strong stimulus for the development of atherosclerotic lesions [107]. Hence, it is not surprising that ECs pathophysiology is precisely regulated by different mechanisms. Among these, ncRNA are recently arousing large interest. Both miRNAs and long noncoding RNAs are expressed in ECs and their expression has been found to be modulated in different conditions, suggesting a potential role of these molecules as modulators.

7. Endothelial miRNAs

7.1. miR-126

The most highly expressed miRNA in ECs is miR-126. It is involved in inflammatory response and endothelial dysfunction [108,109]. Its deletion impairs ECs regeneration in injured arteries [110] and turns out into a loss of vascular integrity and diminished angiogenesis in a murine model [108,109]. miR-126 is able to modulate the action of VEGF and TNF- α, two of the main signaling pathways in ECs, by the inhibition of the sprout-related protein SPRED-1 and the PIK3R kinase, as well as the vascular cell adhesion protein 1 (VCAM-1) [109,111], an inflammatory cytokine that is highly expressed in the early phase of atherosclerosis. miR-126 also modulates ECs response to lipids, and exerts a protective role by modulating ECs turnover [112]. Indeed, miR-126 overexpression promotes ECs proliferation while preventing atherosclerosis through the inhibition of the Notch1 pathway acting on Delta-like 1 homolog (Dlk1) [110]. Moreover, it inhibits leucocytes adhesion through the repression of activated leucocyte cell adhesion molecule (ALCAM) and SetD5 [113], and monocytes recruitment to ox-LDL-injured ECs, preventing the activation of PI3K/Akt/NF-κB pathway [114]. Despite its biological function has not been completely elucidated yet, low levels of this miRNA have been associated to multiple cardiovascular diseases, including acute myocardial infarction, heart failure and CAD [115].

7.2. miR-17/92a cluster

Another key regulator in CAD, also proposed as potential biomarker, is the cluster miR-17/92a. Its levels are upregulated during exercise training in patients undergoing coronary bypass surgery [116], in both rat and mouse models of ischemia and vascular injury [117–119]. This cluster, and miR-92a in particular, negatively regulates vessel growth; its functional inhibition causes an increase in ECs proliferation and migration, and promotes angiogenesis [118,120]. Its action is at least in part mediated by integrin-α5 (ITGA5), and it is sufficient to reduce the restenosis in a rat model of angioplasty [117]. This effect has been further confirmed in the mouse femoral artery injury model. In fact, in this latter model miR-92a inhibition was associated with an acceleration of re-endothelialization and the prevention of neointima formation [121]. These effects were mediated by an increase in the expression levels of ITGA5 and SIRT1 [121].

Interestingly, it has been shown that miR-92a expression is higher in ECs isolated from areas susceptible to atherosclerosis compared to athero-resistant regions [119]. In fact, miR-92a exerts part of its pro-atherosclerotic effect through a fine-tuning regulation of KLF-2 and KLF-4 [119,122]. At the same time, it also regulates the endothelial nitric oxide synthase (eNOS) modulation. The latter is responsible for the production of nitric oxide (NO), which has anti-atherosclerotic properties [123,124], confirming a key role for miR-92a in this process.

7.3. miR-221/222

Of the miRNAs involved in the regulation of NO production in ECs, miR-221/222 are among the 15 most expressed [125] [126]. miR-221/222 inhibit ECs proliferation and migration *in vitro*, as well as new vessel formation, mainly targeting the stem cell marker c-kit [125]. A similar effect has been observed in other cell lines, such as VSMCs and hematopoietic progenitor cells [126,127]. MiR-221/222 exert a cell-specific regulation with apparently opposite effects in ECs and VSMCs, playing a critical role in vascular biology [70]. It was recently demonstrated that miR-222 is involved in cell-to-cell communication. Indeed, it is transferred through endothelial-derived microparticles to remotely modulate intracellular adhesion molecule 1 (ICAM-1) expression [128]. The transfer of functionally active miRNAs though microparticles is also common to other important miRNAs, which modulate the crosstalk between ECs and VSMCs, such as miR126 and miR143/145 [129–131]. Interestingly, it was observed that administration of atorvastatin, a drug used to lower the cholesterol blood levels, downregulates miR-221/222 expression in ECs progenitor obtained from patients with CAD, and is positively correlated to LDL levels, suggesting a contribution of this miRNAs to the effect mediated by statins [132]. In addition, these miRNAs modulate the apoptotic response of ECs to ox-LDL, contributing to atherosclerosis by regulating ETS-1 and the related inflammatory processes [133,134], and participate to inflammation-mediated angiogenesis by targeting the signal transducer and activator of transcription 5A (STAT5A) [135].

7.4. miR-21

Among the miRNAs proposed as biomarkers for CAD, there is miR-21 [136]. This miRNA plays a crucial role in several processes, including development, inflammation and cardiovascular diseases [137]. In ECs, miR-21 mediates angiogenesis through different targets, such as PTEN, SMAD7, type I and type V collagen, and proteoglycan expression *in vitro* [138,139], and it is though to be a mediator of the anti-angiogenetic effect of metformin, a commonly used anti-diabetic drug [138]. Moreover, miR-21 expression is strongly modulated by both unidirectional and oscillatory shear stress, and depending on the specific stimulus it can increase eNOS phosphorylation and NO production or inhibit PPAR-α [140,141]. Finally, it has been observed how miR-21 administration is sufficient to diminish blood pressure in mouse models of hypertension by targeting NOX4 [142].

7.5. miR-16

Peripheral ischemia leads to an increased risk of thrombosis [143]. Recently, our group demonstrated how high levels of miR-16 inhibit RhoGDIα and reduce NO bioavailability exerting a negative effect on endothelial repair and worsening the response to vascular injury in a mouse model of hindlimb ischemia [144]. It is known that miR-16 inhibits ECs proliferation and migration *in vitro* through the vascular endothelial growth factor (VEGF), VEGF receptor-2 (VEGFR2), and the fibroblast growth factor receptor-1 (FGFR1) [145], while it impairs the function of circulating proangiogenic cells *in vivo*. High levels of miR-16 are associated with a higher risk of limb amputation and restenosis in patients with severe limb ischemia, making this miRNA a good candidate as prognostic biomarker in this specific clinical setting [146]. Endothelium-enriched miRNAs involved in biological mechanisms underlying vascular remodeling and restenosis are listed in Table 2.

8. LncRNAs in endothelial cells

8.1. NOS3AS/ATG9B

One of the first ECs-enriched lncRNA to be investigated was an antisense transcript, known as *NOS3AS* or *ATG9B*, that is able to down-regulate eNOS expression [147]. This finding is very interesting, given the key role played by this enzyme in ECs and in vascular remodeling in general. Indeed, as mentioned before, eNOS is responsible for the production of nitric oxide (NO), which has anti-atherosclerotic and antithrombotic properties, promoting a cardio-protective effect [117,123,124,148]. ATG9B is an antisense lncRNA that partially overlaps the *NOS3* gene (coding for eNOS). Its expression is low in human ECs in normal conditions, while it is up-regulated following hypoxia [149].

8.2. HIF-1AS

Hypoxic conditions also modulate eNOS indirectly through the up-regulation of the hypoxia-inducible factor 1 (HIF-1), a protein that regulates cell responses to low concentration of oxygen and is considered a potential target in atherosclerosis [150]. In this respect, another antisense lncRNA, *HIF-1AS*, has been found to be expressed in different human tissues [151], and it is up-regulated in patients with acute myocardial infarction [152]. *HIF1A-AS1* has an anti-proliferative and pro-apoptotic effect on ECs. Interestingly, it seems to be regulated by clopidogrel, a commonly used antiplatelet drug that is able to promote proliferation and reduce apoptosis through the down-regulation of *HIF1A-AS1* [153].

8.3. LEENE

Recently, the lncRNA enhancing eNOS expression (*LEENE*) has been identified in human ECs. It increases the transcription of the eNOS mRNA by facilitating the recruitment of RNA pol II to the enhancer region [154].

8.4. Mantis

A similar mechanism is used by another lncRNA involved in angiogenesis, *MANTIS*. Indeed, this transcript interacts with different proteins including the Subunit BRG1 of SWI/SNF Chromatin-Remodeling Complex, acting as a scaffold to promote endothelial gene transcription, such as SOX18, SMAD6, and COUP-TFII [155]. *MANTIS* down-regulation reduces tube formation and sprouting of ECs *in vitro* and its levels are downregulated in patients with pulmonary arterial hypertension [156].

8.5. HOTAIR

The HOX Antisense Intergenic RNA (*HOTAIR*) that acts as scaffold for PolycombRepressive Complex 2 and LSD1/CoREST/REST complex gives a further example of lncRNA using this mechanism [157,158]. This lncRNA regulates chromatin by means of histone modifications, but it also acts as a scaffold for proteins ubiquitination [159], being involved in several cancer types [160]. In ECs, *HOTAIR* promotes angiogenesis through the VEGFA signaling [161] and enhances cells proliferation and migration during atherosclerosis through PI3K/AKT-IRF1 [162].

8.6. cZNF292

In human ECs, hypoxia also induces the transcription of different other lncRNAs, such as *cZNF292*, *linc00657*, *linc00493*, *MEG3*, *TUG1* and *MALAT1* [163]. Among these, *cZNF292* differs from the others because of its conformation; it belongs to the circularRNA (circRNA) family. In ECs it is up-regulated in response to hypoxic stimuli, possibly through a modulation of the splicing of its original transcript, and promotes angiogenesis and sprouting [164].

8.7. MALAT1

MALAT1 has been initially identified in human cancer cells [165], where it is known also for promoting tumor-induced angiogenesis [166], but then it has also been very well characterized in ECs [163]. In these cells, *Malat1* down-regulation impairs cell proliferation. In line with this observation, it promotes the pro-migratory phenotype *in vitro* and reduces capillary density, blood flow recovery and neonatal vascularization in a mouse model of retinal angiogenesis [163], suggesting a protective role of this lncRNA in ECs. Within this context, high levels of *Malat1* have been found related to diabetes-induced micro-vascular dysfunction in both rats and mice [167], as well as to hyperglycaemia induced inflammatory processes in humans [168]. *MALAT1* also acts through different signaling pathways [168–170], interacting with different miRNAs [153,169,171,172]. Interestingly, *MALAT1* plays a protective role against ox-LDL-induced endothelial dysfunction modulating AKT in patients with unstable angina [170].

8.8. MEG3

Another conserved lncRNA, *Meg3*, has been found to affect endothelial function contrasting angiogenesis through the Notch signaling and the p53/NOX4 axis in rats [173,174]. It is also up-regulated in human senescent ECs and its inhibition reduced aging-related blocking of vessel sprouting [99].

8.9. MIAT

The interaction between lncRNAs and miRNAs is a very common feature among ncRNAs. For example, myocardial infarction associated transcript (*MIAT*) acts as competing endogenous RNA (ceRNA) in several contexts [175–177]. In particular, it modulates miR-150-5p activity and subsequently affects the activation of VEGF, a critical modulator of endothelial function [175]; but it aslo modulates miR-155-5p and miR-22-3p expression, in both mouse and rat models *in vivo*, as well as in human cells *in vitro* [176,177].

8.10. MKI67IP-3

Another example of ceRNA is given by *MKI67IP-3* that counteracts the pro-inflammatory effect induced by the miRNA let-7e in ECs through NF-kB signaling. Let-7e is indeed highly expressed in human ECs in response to ox-LDL and in atherosclerotic plaques, and it induces apoptosis in activated ECs. Interestingly, its effect is inhibited by *MKI67IP-3*, which in turn is down-regulated by let-7e in a positive feedback loop which is critical for modulation of inflammation, vascular remodeling and atherosclerosis [178].

8.11. TGFB2-OT1

Another lncRNA involved in the regulation of inflammatory status is *TGFB2-OT1*. Despite the underlying mechanism is still unclear, this lncRNA has been found involved in both inflammation and autophagy in human vascular ECs. It exerts is effect through the interaction with miR-3960, miR-4488, miR-4459 and the subsequent up-regulation of the inflammatory proteins CERS1, NAT8L and LARP1 [179].

8.12. RNA-RNCR3

Known for being modulated during mouse retina development [180], the *RNA-Rncr3* has been recently found to be up-regulated in atherosclerotic tissues and *in vitro* after the treatment with ox-LDL. It exerts a protective effect promoting apoptosis and inhibiting proliferation, acting as a ceRNA for miR-185-5p and creating a feedback loop with KLF2 [40].

8.13. Tie1-AS

Another transcript playing a critical role in ECs is *Tie1-AS*, an antisense RNA that partially overlaps the 3′UTR of Tie1 and is conserved in human, mouse and zebrafish [181]. This lncRNA modulates angiogenesis. Its overexpression induces a reduction in Tie1 expression levels with a subsequent impairment in vascular development both *in vitro* and *in vivo*, affecting the tube formation ability of ECs, as well as causing defects in cell-cell junctions in zebrafish [181].

8.14. LncRNA known as “TERMINATOR”

Using a cell differentiation model, other lncRNAs implicated in vascular development have been identified, and given the following names by the authors: *TERMINATOR*, *ALIEN* (*Linc00261*) and *PUNISHER (AGAP2-AS1)*. The first one is an intergenic transcript, which controls the pluripotency of stem cells, and its knockdown causes development arrest and lethality [182].

8.15. Linc00261

Long intergenic non-protein coding RNA 261 (*Linc00261*, also known as *DEANR1* or *ALIEN*) correlates with cardiovascular commitment and its knockdown shows a defective vascular patterns and heart chambers defects [182].

8.16. AGAP2-AS1

Finally, the most important lncRNA for the ECs among these is **AGAP2 antisense RNA1** (*AGAP2-AS1*, also known as PUNISHER), an antisense lncRNA which is highly expressed in mature ECSs and regulates their function [182].

8.17. Dll4

Another gene involved in ECs development is Delta-like 4 ligand (*Dll4*), indeed, its modulation affects ECs proliferation and migration. Three different isoforms of antisense RNAs for this gene have been found in both murine and human cells, and despite their precise role is not defined yet, they might act as control mechanism on the haploinsufficiency for this gene, which would cause embryonic lethality [183].

8.18. SENCR

SENCR is highly expressed in both VSMCs and ECs in humans. It is known to stabilize the VSMCs contractile phenotype [94]. However, in ECs *SENCR* promotes proliferation, migration, and angiogenesis *in vitro*, contributing to the differentiation and commitment of ECs [184]. Notably, its expression is altered in patients affected by coronary artery disease or hindlimb ischemia [184], suggesting that this lncRNA plays a different role in vascular cells.

8.19. ANRIL

ANRIL is transcribed from the INK/ARF locus, and is expressed in human VSMCs, ECs and inflammatory cells. Several isoforms have been identified [185], some of which are associated with cell cycle modulation [84,186,187], as well as with the response of ECs fo inflammation [187]. *ANRIL* has been found to be associated with several vascular diseases, including coronary artery disease, myocardial infarction and atherosclerosis [38,84,188,189]. Interestingly, *ANRIL* expression shows a direct correlation with the severity of atherosclerosis [38].

Table 3
Noncoding RNAs as potential biomarkers.

ncRNA	Arterial district	Study size	Change in restenosis	Clinical value	Ref
miR-21	Coronary	181	Increased in ISR	diagnostic of ISR (AUC = 0.568 at ROC)	[56]
miR-92a	Peripheral	62	Increased above 2167 copies/μL	Independent perdictor of TVR (2 years)	[64]
miR-100	Coronary	181	Decreased in ISR	diagnostic of ISR (AUC = 0.608 at ROC)	[56]
miR-133a	Coronary	111	Increased transcoronary gradient	predicts TLR for ISR	[59]
miR-143	Coronary	181	Decreased in ISR	diagnostic of ISR (AUC = 0.818 at ROC)	[56]
miR-143	Peripheral	165	Decreased in ISR	Independent predictor of ISR	[55]
miR-145	Coronary	181	Decreased in ISR	diagnostic of ISR (AUC = 0.880 at ROC)	[56]
miR-195	Peripheral	62	Increased above 263.3 copies/μL	Independent perdictor of TVR (2 years)	[64]

AUC = area under the curve; ISR = In-Stent Restenosis; ROC = receiver operating characteristic curve; TLR = target lesion revascularization; TVR = target vessel revascularization.

8.20. GAS5

Recently, *in vivo* studies showed elevated levels of the lncRNA *GAS5* in atherosclerotic plaques, implying that this lncRNA is involved in atherosclerosis [190]. Furthermore, gain- and loss- of function studies showed how *GAS5* modulates macrophages and ECs apoptosis *in vitro*, and even more interestingly, how it can be carried by extracellular particles, such as exosomes, to other cells of the atherosclerotic plaque [191]. *GAS5* was originally isolated from mice embryonic fibroblasts, but it is widely expressed in adult tissues [192], and it is able to regulate vascular cell function through the β-catenin signaling pathway [193]. Interestingly, *GAS5* is strongly reduced during vascular remodeling in spontaneously hypertensive rats (SHR), a genetic model of hypertension [193]. Nevertheless, its levels are reduced only in patients with coronary artery disease, suggesting a potential role as a biomarker [194].

Representative examples of ncRNAs involved in VSMC phenotypic switch are shown in Fig. 1, while the main lncRNAs known to affect EC function and their mechanisms are listed in Table 2.

9. Clinical perspectives

Although experimental evidence on the role played by lncRNAs in the mechanisms underlying vascular remodeling has been accumulating only very recently, a growing number of promising therapeutic targets are becoming progressively available. This opens up a novel encouraging avenue in the treatment of cardiovascular diseases. In particular, the complex tri-dimensional structure of several lncRNAs allows them to mediate different biological effects, some of which are key biological elements. These characteristics suggest that a large biological impact can be foreseen in the next future through the therapeutic interference with lncRNA.

However, the upcoming clinical application to be exploited in the next years is the use of these regulatory molecules as smart disease biomarkers. Indeed, noncoding RNAs can be released by cells and tissues into the blood, and some of them have shown a high extracellular stability and have been tested with very promising results as biomarkers of in-stent restenosis, both in the coronary tree [56,59] and in the peripheral vascular district [55,64].

Several miRs have already been proposed as disease biomarkers and some are under evaluation in clinical research projects. Although lncRNAs are newcomers in this field, they present some specific characteristics that make them very attractive as potential biomarkers to be exploited for clinical use. In fact, some classes of lncRNAs are potentially more robust markers compared to miRs, which could represent and advantage in terms of clinical exploitation. For example, some lncRNAs “sponge” a substantial number of miRs. Consequently, several miRs are modulated for a single lncRNA, making measurement of the lncRNA more convenient. Furthermore, some lncRNAs have multiple binding sites for different miRs. Hence, measuring one single lncRNAs would allow to indirectly detect a quantum of a specific “pattern” of miRs. As a matter of fact, the evidence that lncRNAs are also packed in microvesicles or exosomes, as noticed earlier for miRs, increases their interest as biomarkers and has a practical impact on their measurement, which should be taken into account in the development of diagnostic toolkits.

Moreover, ncRNAs offer a specific advantage as clinical biomarkers, since they reflect the status of intracellular biological processes. This can have a relevant impact on their capacity to follow up specific biological processes underlying a certain disease or help the etiological diagnosis of a specific disease or clinical syndrome, with obvious impact on therapy and prognosis [20].

Potential clinical applications include both pre-implant prediction of restenosis risk, and diagnosis of already established restenosis [55,56,59,64]. This would potentially offer the chance to implement the pre-procedural planning with a tool that would suggest which patients are at higher risk for in-stent restenosis and could therefore be better candidate to surgical rather that transcatheter revascularization. Although validation is needed in large clinical trials, results from seminal studies using this approach were very promising [56,59,64]. Also, the resulting information could help in selection of the better transcatheter revascularization strategy, including the selection of the most appropriate stent and antiproliferative drug.

Another attracting clinical application would be the noninvasive diagnosis of restenosis once it has already occurred. This latter use would be particularly relevant for the management of patients after percutaneous transcatheter revascularization. In fact, noninvasive tests are not always easy to interpret and they are not able to differentiate *de novo* stenoses or progression of non-target lesions from re-stenotic lesions. In addition, the time window within the risk for restenosis falls can be very variable, depending from individual patients' characteristics, the type of stent used and the pharmacological treatment. This makes the use of invasive tests or costly imaging examinations very difficult to plan. Interestingly, some clinical studies already explored this potentiality with promising results [56]. In fact, as it can be noticed from Table 3, the diagnostic performance of single miRNAs was particularly high in some cases.

The continuous improvement of analytical methods to detect miRNAs will probably give a further momentum to the clinical research on the potential use of circulating miRNAs as diagnostic biomarkers. Indeed, novel diagnostic method that are faster, more reliable and less expensive than traditional quantitative polymerase chain reaction (PCR) are under development. Among the others, faster PCR methods using primers on multi-well plates or microfluidic cards should be mentioned, while other groups are testing alternative methods based on direct hybridization or enzyme-linked assays. Using a different approach, promising diagnostic test are under development using nanosensors coupled with microfluidic platforms, that could allow label-free, reliable, cheap and fast detection methods in the near future [195–198].

References

[1] C. Indolfi, S. De Rosa, A. Colombo, Bioresorbable vascular scaffolds - basic concepts and clinical outcome, Nat. Rev. Cardiol. 13 (2016) 719–729.
[2] C. Indolfi, E. Stabile, C. Perrino, M. Chiariello, Mechanisms of restenosis after angioplasty and approach to therapy (Review), Int. J. Mol. Med. 2 (1998) 143–148.
[3] C. Indolfi, G. Esposito, E. Stabile, L. Cavuto, A. Pisani, C. Coppola, et al., A new rat model of small vessel stenting, Basic Res. Cardiol. 95 (2000) 179–185.
[4] A. Curcio, D. Torella, G. Cuda, C. Coppola, M.C. Faniello, F. Achille, et al., Effect of stent coating alone on in vitro vascular smooth muscle cell proliferation and apoptosis, Am. J. Physiol. Heart Circ. Physiol. 286 (2004) H902–H908.
[5] C. Gareri, S. De Rosa, C. Indolfi, MicroRNAs for Restenosis and Thrombosis After Vascular Injury, Circ. Res. 118 (2016) 1170–1184.
[6] D.L. Fischman, M.B. Leon, D.S. Baim, R.A. Schatz, M.P. Savage, I. Penn, et al., A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators, N. Engl. J. Med. 331 (1994) 496–501.
[7] D.E. Cutlip, M.S. Chauhan, D.S. Baim, K.K. Ho, J.J. Popma, J.P. Carrozza, et al., Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials, J. Am. Coll. Cardiol. 40 (2002) 2082–2089.
[8] A. Mongiardo, A. Curcio, C. Spaccarotella, S. Parise, C. Indolfi, Molecular mechanisms of restenosis after percutaneous peripheral angioplasty and approach to endovascular therapy, Curr. Drug Targets Cardiovasc. Haematol. Disord. 4 (2004) 275–287.
[9] E. Camenzind, P.G. Steg, W. Wijns, Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern, Circulation 115 (2007) 1440–1455 discussion 55.
[10] M. Joner, A.V. Finn, A. Farb, E.K. Mont, F.D. Kolodgie, E. Ladich, et al., Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk, J. Am. Coll. Cardiol. 48 (2006) 193–202.
[11] A. Curcio, D. Torella, C. Indolfi, Mechanisms of smooth muscle cell proliferation and endothelial regeneration after vascular injury and stenting: approach to therapy, Circ. J. 75 (2011) 1287–1296.
[12] C. Iaconetti, C. Gareri, A. Polimeni, C. Indolfi, Non-coding RNAs: the "dark matter" of cardiovascular pathophysiology, Int. J. Mol. Sci. 14 (2013) 19987–20018.
[13] T. Thum, G. Condorelli, Long noncoding RNAs and microRNAs in cardiovascular pathophysiology, Circ. Res. 116 (2015) 751–762.
[14] C. Indolfi, A. Curcio, Stargazing microRNA maps a new miR-21 star for cardiac hypertrophy, J. Clin. Invest. 124 (2014) 1896–1898.
[15] A. Curcio, D. Torella, C. Iaconetti, E. Pasceri, J. Sabatino, S. Sorrentino, et al., MicroRNA-1 downregulation increases connexin 43 displacement and induces ventricular tachyarrhythmias in rodent hypertrophic hearts, PLoS One 8 (2013) e70158.
[16] S. De Rosa, A. Curcio, C. Indolfi, Emerging role of microRNAs in cardiovascular diseases, Circ. J. 78 (2014) 567–575.
[17] S. De Rosa, C. Indolfi, Circulating microRNAs as biomarkers in cardiovascular diseases, EXS 106 (2015) 139–149.
[18] C. Iaconetti, S. Sorrentino, S. De Rosa, C. Indolfi, Exosomal miRNAs in heart disease, Physiology (Bethesda) 31 (2016) 16–24.
[19] A. Carino, S. De Rosa, S. Sorrentino, A. Polimeni, J. Sabatino, G. Caiazzo, et al., Modulation of circulating MicroRNAs levels during the switch from clopidogrel to ticagrelor, Biomed. Res. Int. 2016 (2016) 3968206.
[20] S. De Rosa, F. Eposito, C. Carella, A. Strangio, G. Ammirati, J. Sabatino, et al., Transcoronary concentration gradients of circulating microRNAs in heart failure, Eur. J. Heart Fail. 20 (6) (2018 Jun) 1000–1010, https://doi.org/10.1002/ejhf.1119 Epub 2018 Jan 4.
[21] S. Uchida, S. Dimmeler, Long noncoding RNAs in cardiovascular diseases, Circ. Res. 116 (2015) 737–750.
[22] F. Kopp, J.T. Mendell, Functional classification and experimental dissection of long noncoding RNAs, Cell 172 (2018) 393–407.
[23] I. Gonzalez, R. Munita, E. Agirre, T.A. Dittmer, K. Gysling, T. Misteli, et al., A lncRNA regulates alternative splicing via establishment of a splicing-specific chromatin signature, Nat. Struct. Mol. Biol. 22 (2015) 370–376.
[24] P.J. Batista, H.Y. Chang, Long noncoding RNAs: cellular address codes in development and disease, Cell 152 (2013) 1298–1307.
[25] M. Cesana, D. Cacchiarelli, I. Legnini, T. Santini, O. Sthandier, M. Chinappi, et al., A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA, Cell 147 (2011) 358–369.
[26] P.K. Puvvula, R.D. Desetty, P. Pineau, A. Marchio, A. Moon, A. Dejean, et al., Long noncoding RNA PANDA and scaffold-attachment-factor SAFA control senescence entry and exit, Nat. Commun. 5 (2014) 5323.
[27] Z. Xue, S. Hennelly, B. Doyle, A.A. Gulati, I.V. Novikova, K.Y. Sanbonmatsu, et al., A G-Rich motif in the lncRNA braveheart interacts with a zinc-finger transcription factor to specify the cardiovascular lineage, Mol. Cell 64 (2016) 37–50.
[28] T.B. Hansen, T.I. Jensen, B.H. Clausen, J.B. Bramsen, B. Finsen, C.K. Damgaard, et al., Natural RNA circles function as efficient microRNA sponges, Nature 495 (2013) 384–388.
[29] N. Leveille, C.A. Melo, K. Rooijers, A. Diaz-Lagares, S.A. Melo, G. Korkmaz, et al., Genome-wide profiling of p53-regulated enhancer RNAs uncovers a subset of enhancers controlled by a lncRNA, Nat. Commun. 6 (2015) 6520.
[30] P. Grote, L. Wittler, D. Hendrix, F. Koch, S. Wahrisch, A. Beisaw, et al., The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse, Dev. Cell 24 (2013) 206–214.
[31] M. Sauvageau, L.A. Goff, S. Lodato, B. Bonev, A.F. Groff, C. Gerhardinger, et al., Multiple knockout mouse models reveal lincRNAs are required for life and brain development, elife 2 (2013) e01749.
[32] J. Beermann, D. Kirste, K. Iwanov, D. Lu, F. Kleemiss, R. Kumarswamy, et al., A large shRNA library approach identifies lncRNA Ntep as an essential regulator of cell proliferation, Cell Death Differ. 25 (2018) 307–318.
[33] L.L. Chen, Linking long noncoding RNA localization and function, Trends Biochem. Sci. 41 (2016) 761–772.
[34] J. Wang, X. Liu, H. Wu, P. Ni, Z. Gu, Y. Qiao, et al., CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer, Nucleic Acids Res. 38 (2010) 5366–5383.
[35] M. Kretz, D.E. Webster, R.J. Flockhart, C.S. Lee, A. Zehnder, V. Lopez-Pajares, et al., Suppression of progenitor differentiation requires the long noncoding RNA ANCR, Genes Dev. 26 (2012) 338–343.
[36] S.T. da Rocha, V. Boeva, M. Escamilla-Del-Arenal, K. Ancelin, C. Granier, N.R. Matias, et al., Jarid2 is implicated in the initial xist-induced targeting of PRC2 to the inactive X chromosome, Mol. Cell 53 (2014) 301–316.
[37] F. Bardou, F. Ariel, C.G. Simpson, N. Romero-Barrios, P. Laporte, S. Balzergue, et al., Long noncoding RNA modulates alternative splicing regulators in Arabidopsis, Dev. Cell 30 (2014) 166–176.
[38] L.M. Holdt, F. Beutner, M. Scholz, S. Gielen, G. Gabel, H. Bergert, et al., ANRIL expression is associated with atherosclerosis risk at chromosome 9p21, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 620–627.
[39] G. Wu, J. Cai, Y. Han, J. Chen, Z.P. Huang, C. Chen, et al., LincRNA-p21 regulates neointima formation, vascular smooth muscle cell proliferation, apoptosis, and atherosclerosis by enhancing p53 activity, Circulation 130 (2014) 1452–1465.
[40] K. Shan, Q. Jiang, X.Q. Wang, Y.N. Wang, H. Yang, M.D. Yao, et al., Role of long non-coding RNA-RNCR3 in atherosclerosis-related vascular dysfunction, Cell Death Dis. 7 (2016) e2248.
[41] J.E. O'Brien Jr., N. Kibiryeva, X.G. Zhou, J.A. Marshall, G.K. Lofland, M. Artman, et al., Noncoding RNA expression in myocardium from infants with tetralogy of Fallot, Circ. Cardiovasc. Genet. 5 (2012) 279–286.
[42] J.H. Lee, C. Gao, G. Peng, C. Greer, S. Ren, Y. Wang, et al., Analysis of transcriptome complexity through RNA sequencing in normal and failing murine hearts, Circ. Res. 109 (2011) 1332–1341.
[43] L. Korostowski, N. Sedlak, N. Engel, The Kcnq1ot1 long non-coding RNA affects chromatin conformation and expression of Kcnq1, but does not regulate its imprinting in the developing heart, PLoS Genet. 8 (2012) e1002956.
[44] Y. Cai, Y. Yang, X. Chen, G. Wu, X. Zhang, Y. Liu, et al., Circulating 'lncRNA OTTHUMT00000387022' from monocytes as a novel biomarker for coronary artery disease, Cardiovasc. Res. 112 (2016) 714–724.
[45] A.S. Schaefer, G. Bochenek, A. Jochens, D. Ellinghaus, H. Dommisch, E. Guzeldemir-Akcakanat, et al., Genetic evidence for PLASMINOGEN as a shared genetic risk factor of coronary artery disease and periodontitis, Circ. Cardiovasc. Genet. 8 (2015) 159–167.
[46] D. Torella, C. Iaconetti, D. Catalucci, G.M. Ellison, A. Leone, C.D. Waring, et al., MicroRNA-133 controls vascular smooth muscle cell phenotypic switch in vitro and vascular remodeling in vivo, Circ. Res. 109 (2011) 880–893.
[47] A. Polimeni, S. De Rosa, C. Indolfi, Vascular miRNAs after balloon angioplasty, Trends Cardiovasc. Med. 23 (2013) 9–14.
[48] D. Gomez, G.K. Owens, Smooth muscle cell phenotypic switching in atherosclerosis, Cardiovasc. Res. 95 (2012) 156–164.
[49] L.S. Shankman, D. Gomez, O.A. Cherepanova, M. Salmon, G.F. Alencar, R.M. Haskins, et al., KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis, Nat. Med. 21 (2015) 628–637.
[50] S.M. Schwartz, Smooth muscle migration in atherosclerosis and restenosis, J. Clin. Invest. 100 (1997) S87–S89.
[51] K.R. Cordes, N.T. Sheehy, M.P. White, E.C. Berry, S.U. Morton, A.N. Muth, et al., miR-145 and miR-143 regulate smooth muscle cell fate and plasticity, Nature 460 (2009) 705–710.
[52] L. Elia, M. Quintavalle, J. Zhang, R. Contu, L. Cossu, M.V. Latronico, et al., The knockout of miR-143 and -145 alters smooth muscle cell maintenance and vascular homeostasis in mice: correlates with human disease, Cell Death Differ. 16 (2009) 1590–1598.
[53] Y. Cheng, X. Liu, J. Yang, Y. Lin, D.Z. Xu, Q. Lu, et al., MicroRNA-145, a novel smooth muscle cell phenotypic marker and modulator, controls vascular neointimal lesion formation, Circ. Res. 105 (2009) 158–166.
[54] M. Quintavalle, L. Elia, G. Condorelli, S.A. Courtneidge, MicroRNA control of podosome formation in vascular smooth muscle cells in vivo and in vitro, J. Cell Biol. 189 (2010) 13–22.
[55] Z.H. Yu, H.T. Wang, C. Tu, Diagnostic value of microRNA-143 in predicting in-stent restenosis for patients with lower extremity arterial occlusive disease, Eur. J. Med. Res. 22 (2017) 2.
[56] M. He, Y. Gong, J. Shi, Z. Pan, H. Zou, D. Sun, et al., Plasma microRNAs as potential noninvasive biomarkers for in-stent restenosis, PLoS One 9 (2014) e112043.
[57] H. Zhao, G. Wen, Y. Huang, X. Yu, Q. Chen, T.A. Afzal, et al., MicroRNA-22 regulates smooth muscle cell differentiation from stem cells by targeting methyl CpG-binding protein 2, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 918–929.
[58] F. Yang, Q. Chen, S. He, M. Yang, E.M. Maguire, W. An, et al., miRNA-22 is a novel mediator of vascular smooth muscle cell phenotypic modulation and neointima formation, Circulation 137 (17) (2018 Apr 24) 1824–1841, https://doi.org/10.1161/CIRCULATIONAHA.117.027799 Epub 2017 Dec 15.
[59] R. De Rosa, S. De Rosa, D. Leistner, J.N. Boeckel, T. Keller, S. Fichtlscherer, et al., Transcoronary concentration gradient of microRNA-133a and outcome in patients With coronary artery disease, Am. J. Cardiol. 120 (2017) 15–24.

[60] C. Iaconetti, S. De Rosa, A. Polimeni, S. Sorrentino, C. Gareri, A. Carino, et al., Down-regulation of miR-23b induces phenotypic switching of vascular smooth muscle cells in vitro and in vivo, Cardiovasc. Res. 107 (2015) 522–533.
[61] C. Gareri, C. Iaconetti, S. Sorrentino, C. Covello, S. De Rosa, C. Indolfi, miR-125a-5p modulates phenotypic switch of vascular smooth muscle cells by targeting ETS-1, J. Mol. Biol. 429 (2017) 1817–1828.
[62] Y.S. Wang, H.Y. Wang, Y.C. Liao, P.C. Tsai, K.C. Chen, H.Y. Cheng, et al., MicroRNA-195 regulates vascular smooth muscle cell phenotype and prevents neointimal formation, Cardiovasc. Res. 95 (2012) 517–526.
[63] P. Li, N. Zhu, B. Yi, N. Wang, M. Chen, X. You, et al., MicroRNA-663 regulates human vascular smooth muscle cell phenotypic switch and vascular neointimal formation, Circ. Res. 113 (2013) 1117–1127.
[64] S. Stojkovic, M. Jurisic, C.W. Kopp, R. Koppensteiner, K. Huber, J. Wojta, et al., Circulating microRNAs identify patients at increased risk of in-stent restenosis after peripheral angioplasty with stent implantation, Atherosclerosis 269 (2018) 197–203.
[65] O. Ham, S.Y. Lee, B.W. Song, C.Y. Lee, J. Lee, H.H. Seo, et al., Small molecule-mediated induction of miR-9 suppressed vascular smooth muscle cell proliferation and neointima formation after balloon injury, Oncotarget 8 (2017) 93360–93372.
[66] B. Xie, C. Zhang, K. Kang, S. Jiang, miR-599 inhibits vascular smooth muscle cells proliferation and migration by targeting TGFB2, PLoS One 10 (2015) e0141512.
[67] R. Ji, Y. Cheng, J. Yue, J. Yang, X. Liu, H. Chen, et al., MicroRNA expression signature and antisense-mediated depletion reveal an essential role of MicroRNA in vascular neointimal lesion formation, Circ. Res. 100 (2007) 1579–1588.
[68] R.A. McDonald, C.A. Halliday, A.M. Miller, L.A. Diver, R.S. Dakin, J. Montgomery, et al., Reducing in-stent restenosis: therapeutic manipulation of miRNA in vascular remodeling and inflammation, J. Am. Coll. Cardiol. 65 (2015) 2314–2327.
[69] D. Wang, T. Deuse, M. Stubbendorff, E. Chernogubova, R.G. Erben, S.M. Eken, et al., Local MicroRNA modulation using a novel anti-miR-21-eluting stent effectively prevents experimental in-stent restenosis, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 1945–1953.
[70] X. Liu, Y. Cheng, J. Yang, L. Xu, C. Zhang, Cell-specific effects of miR-221/222 in vessels: molecular mechanism and therapeutic application, J. Mol. Cell. Cardiol. 52 (2012) 245–255.
[71] D.J.J. Lightell, S.C. Moss, T.C. Woods, Upregulation of miR-221 and -222 in response to increased extracellular signal-regulated kinases 1/2 activity exacerbates neointimal hyperplasia in diabetes mellitus, Atherosclerosis (2018) 71–78.
[72] S.G. Sun, B. Zheng, M. Han, X.M. Fang, H.X. Li, S.B. Miao, et al., miR-146a and Kruppel-like factor 4 form a feedback loop to participate in vascular smooth muscle cell proliferation, EMBO Rep. 12 (2011) 56–62.
[73] H. Sun, S. Cai, M. Zhang, J. Zhao, S. Wei, Y. Luo, et al., MicroRNA-206 regulates vascular smooth muscle cell phenotypic switch and vascular neointimal formation, Cell Biol. Int. 41 (2017) 739–748.
[74] T.J. Li, Y.L. Chen, C.J. Gua, S.J. Xue, S.M. Ma, X.D. Li, MicroRNA 181b promotes vascular smooth muscle cells proliferation through activation of PI3K and MAPK pathways, Int. J. Clin. Exp. Pathol. 8 (2015) 10375–10384.
[75] X. Liu, Y. Cheng, X. Chen, J. Yang, L. Xu, C. Zhang, MicroRNA-31 regulated by the extracellular regulated kinase is involved in vascular smooth muscle cell growth via large tumor suppressor homolog 2, J. Biol. Chem. 286 (2011) 42371–42380.
[76] J. Wang, C.H. Yan, Y. Li, K. Xu, X.X. Tian, C.F. Peng, et al., MicroRNA-31 controls phenotypic modulation of human vascular smooth muscle cells by regulating its target gene cellular repressor of E1A-stimulated genes, Exp. Cell Res. 319 (2013) 1165–1175.
[77] X. Yang, M. Dong, H. Wen, X. Liu, M. Zhang, L. Ma, et al., MiR-26a contributes to the PDGF-BB-induced phenotypic switch of vascular smooth muscle cells by suppressing Smad1, Oncotarget 8 (2017) 75844–75853.
[78] C. Chen, Y. Yan, X. Liu, microRNA-612 is downregulated by platelet-derived growth factor-BB treatment and has inhibitory effects on vascular smooth muscle cell proliferation and migration via directly targeting AKT2, Exp. Ther. Med. 15 (2018) 159–165.
[79] F. Xu, A.S. Ahmed, X. Kang, G. Hu, F. Liu, W. Zhang, et al., MicroRNA-15b/16 attenuates vascular neointima formation by promoting the contractile phenotype of vascular smooth muscle through targeting YAP, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 2145–2152.
[80] X. Wang, G. Hu, X. Gao, Y. Wang, W. Zhang, E.Y. Harmon, et al., The induction of yes-associated protein expression after arterial injury is crucial for smooth muscle phenotypic modulation and neointima formation, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2662–2669.
[81] A. Leung, C. Trac, W. Jin, L. Lanting, A. Akbany, P. Saetrom, et al., Novel long noncoding RNAs are regulated by angiotensin II in vascular smooth muscle cells, Circ. Res. 113 (2013) 266–278.
[82] X. Liu, Y. Cheng, S. Zhang, Y. Lin, J. Yang, C. Zhang, A necessary role of miR-221 and miR-222 in vascular smooth muscle cell proliferation and neointimal hyperplasia, Circ. Res. 104 (2009) 476–487.
[83] D.K. Han, Z.Z. Khaing, R.A. Pollock, C.C. Haudenschild, G. Liau, H19, a marker of developmental transition, is reexpressed in human atherosclerotic plaques and is regulated by the insulin family of growth factors in cultured rabbit smooth muscle cells, J. Clin. Invest. 97 (1996) 1276–1285.
[84] A. Congrains, K. Kamide, R. Oguro, O. Yasuda, K. Miyata, E. Yamamoto, et al., Genetic variants at the 9p21 locus contribute to atherosclerosis through modulation of ANRIL and CDKN2A/B, Atherosclerosis 220 (2012) 449–455.
[85] A. Keniry, D. Oxley, P. Monnier, M. Kyba, L. Dandolo, G. Smits, et al., The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r, Nat. Cell Biol. 14 (2012) 659–665.
[86] Z. Ding, X. Wang, L. Schnackenberg, M. Khaidakov, S. Liu, S. Singla, et al., Regulation of autophagy and apoptosis in response to ox-LDL in vascular smooth muscle cells, and the modulatory effects of the microRNA hsa-let-7 g, Int. J. Cardiol. 168 (2013) 1378–1385.
[87] A.N. Kallen, X.B. Zhou, J. Xu, C. Qiao, J. Ma, L. Yan, et al., The imprinted H19 lncRNA antagonizes let-7 microRNAs, Mol. Cell 52 (2013) 101–112.
[88] J. Lv, L. Wang, J. Zhang, R. Lin, L. Wang, W. Sun, et al., Long noncoding RNA H19-derived miR-675 aggravates restenosis by targeting PTEN, Biochem. Biophys. Res. Commun. 497 (4) (2018 Mar 18) 1154–1161, https://doi.org/10.1016/j.bbrc.2017.01.011 Epub 2017 Jan 4.
[89] E. Pasmant, A. Sabbagh, J. Masliah-Planchon, N. Ortonne, I. Laurendeau, L. Melin, et al., Role of noncoding RNA ANRIL in genesis of plexiform neurofibromas in neurofibromatosis type 1, J. Natl. Cancer Inst. 103 (2011) 1713–1722.
[90] D. Vigetti, S. Deleonibus, P. Moretto, T. Bowen, J.W. Fischer, M. Grandoch, et al., Natural antisense transcript for hyaluronan synthase 2 (HAS2-AS1) induces transcription of HAS2 via protein O-GlcNAcylation, J. Biol. Chem. 289 (2014) 28816–28826.
[91] R. Riessen, T.N. Wight, C. Pastore, C. Henley, J.M. Isner, Distribution of hyaluronan during extracellular matrix remodeling in human restenotic arteries and balloon-injured rat carotid arteries, Circulation 93 (1996) 1141–1147.
[92] S. Chai, Q. Chai, C.C. Danielsen, P. Hjorth, J.R. Nyengaard, T. Ledet, et al., Overexpression of hyaluronan in the tunica media promotes the development of atherosclerosis, Circ. Res. 96 (2005) 583–591.
[93] M.D. Ballantyne, K. Pinel, R. Dakin, A.T. Vesey, L. Diver, R. Mackenzie, et al., Smooth muscle enriched long noncoding RNA (SMILR) regulates cell proliferation, Circulation 133 (2016) 2050–2065.
[94] R.D. Bell, X. Long, M. Lin, J.H. Bergmann, V. Nanda, S.L. Cowan, et al., Identification and initial functional characterization of a human vascular cell-enriched long noncoding RNA, Arterioscler. Thromb. Vasc. Biol. 34 (2014) 1249–1259.
[95] Z.Q. Zou, J. Xu, L. Li, Y.S. Han, Down-regulation of SENCR promotes smooth muscle cells proliferation and migration in db/db mice through up-regulation of FoxO1 and TRPC6, Biomed. Pharmacother. 74 (2015) 35–41.
[96] Y. Zhao, G. Feng, Y. Wang, Y. Yue, W. Zhao, Regulation of apoptosis by long non-coding RNA HIF1A-AS1 in VSMCs: implications for TAA pathogenesis, Int. J. Clin. Exp. Pathol. 7 (2014) 7643–7652.
[97] L. Li, X. Li, The E, L.J. Wang, T.Y. Yuan, S.Y. Wang, et al., Low expression of lncRNA-GAS5 is implicated in human primary varicose great saphenous veins, PLoS One 10 (2015) e0120550.
[98] R. Tang, G. Zhang, Y.C. Wang, X. Mei, S.Y. Chen, The long non-coding RNA GAS5 regulates transforming growth factor beta (TGF-beta)-induced smooth muscle cell differentiation via RNA Smad-binding elements, J. Biol. Chem. 292 (2017) 14270–14278.
[99] R.A. Boon, P. Hofmann, K.M. Michalik, N. Lozano-Vidal, D. Berghauser, A. Fischer, et al., Long noncoding RNA Meg3 controls endothelial cell aging and function: implications for regenerative angiogenesis, J. Am. Coll. Cardiol. 68 (2016) 2589–2591.
[100] W. Liu, X. Liu, M. Luo, X. Liu, Q. Luo, H. Tao, et al., dNK derived IFN-gamma mediates VSMC migration and apoptosis via the induction of LncRNA MEG3: a role in uterovascular transformation, Placenta 50 (2017) 32–39.
[101] Z. Sun, X. Nie, S. Sun, S. Dong, C. Yuan, Y. Li, et al., Long Non-Coding RNA MEG3 Downregulation Triggers Human Pulmonary Artery Smooth Muscle Cell Proliferation and Migration via the p53 Signaling Pathway, Cell. Physiol. Biochem. 42 (2017) 2569–2581.
[102] J. Zhao, W. Zhang, M. Lin, W. Wu, P. Jiang, E. Tou, et al., MYOSLID is a novel serum response factor-dependent long noncoding RNA that amplifies the vascular smooth muscle differentiation program, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 2088–2099.
[103] J.M. Miano, Myocardin in biology and disease, J. Biomed. Res. 29 (2015) 3–19.
[104] C.K. Yu, T. Xu, R.K. Assoian, D.J. Rader, Mining the stiffness-sensitive transcriptome in human vascular smooth muscle cells identifies long noncoding RNA stiffness regulators, Arterioscler. Thromb. Vasc. Biol. 38 (2018) 164–173.
[105] L. Jin, X. Lin, L. Yang, X. Fan, W. Wang, S. Li, et al., AK098656, a novel vascular smooth muscle cell-dominant long noncoding RNA, promotes hypertension, Hypertension 71 (2018) 262–272.
[106] P. Neth, M. Nazari-Jahantigh, A. Schober, C. Weber, MicroRNAs in flow-dependent vascular remodelling, Cardiovasc. Res. 99 (2013) 294–303.
[107] J.P. Halcox, W.H. Schenke, G. Zalos, R. Mincemoyer, A. Prasad, M.A. Waclawiw, et al., Prognostic value of coronary vascular endothelial dysfunction, Circulation 106 (2002) 653–658.
[108] S. Wang, A.B. Aurora, B.A. Johnson, X. Qi, J. McAnally, J.A. Hill, et al., The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis, Dev. Cell 15 (2008) 261–271.
[109] J.E. Fish, M.M. Santoro, S.U. Morton, S. Yu, R.F. Yeh, J.D. Wythe, et al., miR-126 regulates angiogenic signaling and vascular integrity, Dev. Cell 15 (2008) 272–284.
[110] A. Schober, M. Nazari-Jahantigh, Y. Wei, K. Bidzhekov, F. Gremse, J. Grommes, et al., MicroRNA-126-5p promotes endothelial proliferation and limits atherosclerosis by suppressing Dlk1, Nat. Med. 20 (2014) 368–376.
[111] T.A. Harris, M. Yamakuchi, M. Ferlito, J.T. Mendell, C.J. Lowenstein, MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 1516–1521.
[112] Y. Wei, M. Nazari-Jahantigh, P. Neth, C. Weber, A. Schober, MicroRNA-126, −145, and −155: a therapeutic triad in atherosclerosis? Arterioscler. Thromb. Vasc. Biol. 33 (2013) 449–454.
[113] L. Poissonnier, G. Villain, F. Soncin, V. Mattot, miR126-5p repression of ALCAM and SetD5 in endothelial cells regulates leucocyte adhesion and transmigration, Cardiovasc. Res. 102 (2014) 436–447.

[114] X. Yuan, J. Chen, M. Dai, Paeonol promotes microRNA-126 expression to inhibit monocyte adhesion to ox-LDL-injured vascular endothelial cells and block the activation of the PI3K/Akt/NF-kappaB pathway, Int. J. Mol. Med. 38 (2016) 1871–1878.
[115] S. Fichtlscherer, A.M. Zeiher, S. Dimmeler, Circulating microRNAs: biomarkers or mediators of cardiovascular diseases? Arterioscler. Thromb. Vasc. Biol. 31 (2011) 2383–2390.
[116] C. Taurino, W.H. Miller, M.W. McBride, J.D. McClure, R. Khanin, M.U. Moreno, et al., Gene expression profiling in whole blood of patients with coronary artery disease, Clin. Sci. (Lond.) 119 (2010) 335–343.
[117] C. Iaconetti, A. Polimeni, S. Sorrentino, J. Sabatino, G. Pironti, G. Esposito, et al., Inhibition of miR-92a increases endothelial proliferation and migration in vitro as well as reduces neointimal proliferation in vivo after vascular injury, Basic Res. Cardiol. 107 (2012) 296.
[118] A. Bonauer, G. Carmona, M. Iwasaki, M. Mione, M. Koyanagi, A. Fischer, et al., MicroRNA-92a controls angiogenesis and functional recovery of ischemic tissues in mice, Science 324 (2009) 1710–1713.
[119] W. Wu, H. Xiao, A. Laguna-Fernandez, G. Villarreal Jr., K.C. Wang, G.G. Geary, et al., Flow-dependent regulation of kruppel-like factor 2 is mediated by MicroRNA-92a, Circulation 124 (2011) 633–641.
[120] C. Doebele, A. Bonauer, A. Fischer, A. Scholz, Y. Reiss, C. Urbich, et al., Members of the microRNA-17-92 cluster exhibit a cell-intrinsic antiangiogenic function in endothelial cells, Blood 115 (2010) 4944–4950.
[121] J.M. Daniel, D. Penzkofer, R. Teske, J. Dutzmann, A. Koch, W. Bielenberg, et al., Inhibition of miR-92a improves re-endothelialization and prevents neointima formation following vascular injury, Cardiovasc. Res. 103 (2014) 564–572.
[122] Y. Fang, P.F. Davies, Site-specific microRNA-92a regulation of Kruppel-like factors 4 and 2 in atherosusceptible endothelium, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 979–987.
[123] C. Maccallini, A. Mollica, R. Amoroso, The positive regulation of eNOS signaling by PPAR agonists in cardiovascular diseases, Am. J. Cardiovasc. Drugs 17 (2017) 273–281.
[124] C. Indolfi, D. Torella, C. Coppola, A. Curcio, F. Rodriguez, A. Bilancio, et al., Physical training increases eNOS vascular expression and activity and reduces restenosis after balloon angioplasty or arterial stenting in rats, Circ. Res. 91 (2002) 1190–1197.
[125] L. Poliseno, A. Tuccoli, L. Mariani, M. Evangelista, L. Citti, K. Woods, et al., MicroRNAs modulate the angiogenic properties of HUVECs, Blood 108 (2006) 3068–3071.
[126] Y. Suarez, C. Fernandez-Hernando, J.S. Pober, W.C. Sessa, Dicer dependent microRNAs regulate gene expression and functions in human endothelial cells, Circ. Res. 100 (2007) 1164–1173.
[127] J. Matsui, T. Wakabayashi, M. Asada, K. Yoshimatsu, M. Okada, Stem cell factor/c-kit signaling promotes the survival, migration, and capillary tube formation of human umbilical vein endothelial cells, J. Biol. Chem. 279 (2004) 18600–18607.
[128] F. Jansen, X. Yang, K. Baumann, D. Przybilla, T. Schmitz, A. Flender, et al., Endothelial microparticles reduce ICAM-1 expression in a microRNA-222-dependent mechanism, J. Cell. Mol. Med. 19 (2015) 2202–2214.
[129] M. Climent, M. Quintavalle, M. Miragoli, J. Chen, G. Condorelli, L. Elia, TGFbeta Triggers miR-143/145 transfer from smooth muscle cells to endothelial cells, thereby modulating vessel stabilization, Circ. Res. 116 (2015) 1753–1764.
[130] E. Hergenreider, S. Heydt, K. Treguer, T. Boettger, A.J. Horrevoets, A.M. Zeiher, et al., Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs, Nat. Cell Biol. 14 (2012) 249–256.
[131] A. Zernecke, K. Bidzhekov, H. Noels, E. Shagdarsuren, L. Gan, B. Denecke, et al., Delivery of microRNA-126 by apoptotic bodies induces CXCL12-dependent vascular protection, Sci. Signal. 2 (2009) ra81.
[132] Y. Minami, M. Satoh, C. Maesawa, Y. Takahashi, T. Tabuchi, T. Itoh, et al., Effect of atorvastatin on microRNA 221/222 expression in endothelial progenitor cells obtained from patients with coronary artery disease, Eur. J. Clin. Investig. 39 (2009) 359–367.
[133] N. Zhu, D. Zhang, S. Chen, X. Liu, L. Lin, X. Huang, et al., Endothelial enriched microRNAs regulate angiotensin II-induced endothelial inflammation and migration, Atherosclerosis 215 (2011) 286–293.
[134] B. Qin, Y. Cao, H. Yang, B. Xiao, Z. Lu, MicroRNA-221/222 regulate ox-LDL-induced endothelial apoptosis via Ets-1/p21 inhibition, Mol. Cell. Biochem. 405 (2015) 115–124.
[135] P. Dentelli, A. Rosso, F. Orso, C. Olgasi, D. Taverna, M.F. Brizzi, microRNA-222 controls neovascularization by regulating signal transducer and activator of transcription 5A expression, Arterioscler. Thromb. Vasc. Biol. 30 (2010) 1562–1568.
[136] F. Jansen, X. Yang, S. Proebsting, M. Hoelscher, D. Przybilla, K. Baumann, et al., MicroRNA expression in circulating microvesicles predicts cardiovascular events in patients with coronary artery disease, J. Am. Heart Assoc. 3 (2014) e001249.
[137] R. Kumarswamy, I. Volkmann, T. Thum, Regulation and function of miRNA-21 in health and disease, RNA Biol. 8 (2011) 706–713.
[138] M. Luo, X. Tan, L. Mu, Y. Luo, R. Li, X. Deng, et al., MiRNA-21 mediates the antiangiogenic activity of metformin through targeting PTEN and SMAD7 expression and PI3K/AKT pathway, Sci. Rep. 7 (2017) 43427.
[139] Z. Wu, Y. He, D. Li, X. Fang, T. Shang, H. Zhang, et al., Long noncoding RNA MEG3 suppressed endothelial cell proliferation and migration through regulating miR-21, Am. J. Transl. Res. 9 (2017) 3326–3335.
[140] M. Weber, M.B. Baker, J.P. Moore, C.D. Searles, MiR-21 is induced in endothelial cells by shear stress and modulates apoptosis and eNOS activity, Biochem. Biophys. Res. Commun. 393 (2010) 643–648.
[141] J. Zhou, K.C. Wang, W. Wu, S. Subramaniam, J.Y. Shyy, J.J. Chiu, et al., MicroRNA-21 targets peroxisome proliferators-activated receptor-alpha in an autoregulatory loop to modulate flow-induced endothelial inflammation, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 10355–10360.
[142] A.J. Kriegel, M.A. Baker, Y. Liu, P. Liu, A.W. Cowley Jr., M. Liang, Endogenous microRNAs in human microvascular endothelial cells regulate mRNAs encoded by hypertension-related genes, Hypertension 66 (2015) 793–799.
[143] G. Brevetti, V. Schiano, S. Verdoliva, A. Silvestro, G. Sirico, J. De Maio, et al., Peripheral arterial disease and cardiovascular risk in Italy. Results of the Peripheral Arteriopathy and Cardiovascular Events (PACE) study, J. Cardiovasc. Med. (Hagerstown) 7 (2006) 608–613.
[144] S. Sorrentino, C. Iaconetti, S. De Rosa, A. Polimeni, J. Sabatino, C. Gareri, et al., Hindlimb ischemia impairs endothelial recovery and increases neointimal proliferation in the carotid artery, Sci. Rep. 8 (2018) 761.
[145] A. Chamorro-Jorganes, E. Araldi, L.O. Penalva, D. Sandhu, C. Fernandez-Hernando, Y. Suarez, MicroRNA-16 and microRNA-424 regulate cell-autonomous angiogenic functions in endothelial cells via targeting vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 2595–2606.
[146] G. Spinetti, O. Fortunato, A. Caporali, S. Shantikumar, M. Marchetti, M. Meloni, et al., MicroRNA-15a and microRNA-16 impair human circulating proangiogenic cell functions and are increased in the proangiogenic cells and serum of patients with critical limb ischemia, Circ. Res. 112 (2013) 335–346.
[147] G.B. Robb, A.R. Carson, S.C. Tai, J.E. Fish, S. Singh, T. Yamada, et al., Post-transcriptional regulation of endothelial nitric-oxide synthase by an overlapping antisense mRNA transcript, J. Biol. Chem. 279 (2004) 37982–37996.
[148] D. Torella, D. Leosco, C. Indolfi, A. Curcio, C. Coppola, G.M. Ellison, et al., Aging exacerbates negative remodeling and impairs endothelial regeneration after balloon injury, Am. J. Physiol. Heart Circ. Physiol. 287 (2004) H2850–H2860.
[149] J.E. Fish, C.C. Matouk, E. Yeboah, S.C. Bevan, M. Khan, K. Patil, et al., Hypoxia-inducible expression of a natural cis-antisense transcript inhibits endothelial nitric-oxide synthase, J. Biol. Chem. 282 (2007) 15652–15666.
[150] T. Jain, E.A. Nikolopoulou, Q. Xu, A. Qu, Hypoxia inducible factor as a therapeutic target for atherosclerosis, Pharmacol. Ther. 183 (2018 Mar) 22–33, https://doi.org/10.1016/j.pharmthera.2017.09.003 Epub 2017 Sep 20.
[151] F. Rossignol, C. Vache, E. Clottes, Natural antisense transcripts of hypoxia-inducible factor 1alpha are detected in different normal and tumour human tissues, Gene 299 (2002) 135–140.
[152] M. Vausort, D.R. Wagner, Y. Devaux, Long noncoding RNAs in patients with acute myocardial infarction, Circ. Res. 115 (2014) 668–677.
[153] X. Wang, M. Li, Z. Wang, S. Han, X. Tang, Y. Ge, et al., Silencing of long noncoding RNA MALAT1 by miR-101 and miR-217 inhibits proliferation, migration, and invasion of esophageal squamous cell carcinoma cells, J. Biol. Chem. 290 (2015) 3925–3935.
[154] Y. Miao, N.E. Ajami, T.S. Huang, F.M. Lin, C.H. Lou, Y.T. Wang, et al., Enhancer-associated long non-coding RNA LEENE regulates endothelial nitric oxide synthase and endothelial function, Nat. Commun. 9 (2018) 292.
[155] M.S. Leisegang, C. Fork, I. Josipovic, F.M. Richter, J. Preussner, J. Hu, et al., Long Noncoding RNA MANTIS Facilitates Endothelial Angiogenic Function, Circulation 136 (2017) 65–79.
[156] M. Rabinovitch, Molecular pathogenesis of pulmonary arterial hypertension, J. Clin. Invest. 122 (2012) 4306–4313.
[157] M.C. Tsai, O. Manor, Y. Wan, N. Mosammaparast, J.K. Wang, F. Lan, et al., Long noncoding RNA as modular scaffold of histone modification complexes, Science 329 (2010) 689–693.
[158] R.A. Gupta, N. Shah, K.C. Wang, J. Kim, H.M. Horlings, D.J. Wong, et al., Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis, Nature 464 (2010) 1071–1076.
[159] J.H. Yoon, K. Abdelmohsen, J. Kim, X. Yang, J.L. Martindale, K. Tominaga-Yamanaka, et al., Scaffold function of long non-coding RNA HOTAIR in protein ubiquitination, Nat. Commun. 4 (2013) 2939.
[160] M. Hajjari, A. Salavaty, HOTAIR: an oncogenic long non-coding RNA in different cancers, Cancer Biol. Med. 12 (2015) 1–9.
[161] X. Ma, Z. Li, T. Li, L. Zhu, Z. Li, N. Tian, Long non-coding RNA HOTAIR enhances angiogenesis by induction of VEGFA expression in glioma cells and transmission to endothelial cells via glioma cell derived-extracellular vesicles, Am. J. Transl. Res. 9 (2017) 5012–5021.
[162] Y. Peng, K. Meng, L. Jiang, Y. Zhong, Y. Yang, Y. Lan, et al., Thymic stromal lymphopoietin-induced HOTAIR activation promotes endothelial cell proliferation and migration in atherosclerosis, Biosci. Rep. 37 (2017).
[163] K.M. Michalik, X. You, Y. Manavski, A. Doddaballapur, M. Zornig, T. Braun, et al., Long noncoding RNA MALAT1 regulates endothelial cell function and vessel growth, Circ. Res. 114 (2014) 1389–1397.
[164] J.N. Boeckel, N. Jae, A.W. Heumuller, W. Chen, R.A. Boon, K. Stellos, et al., Identification and characterization of hypoxia-regulated endothelial circular RNA, Circ. Res. 117 (2015) 884–890.
[165] P. Ji, S. Diederichs, W. Wang, S. Boing, R. Metzger, P.M. Schneider, et al., MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer, Oncogene 22 (2003) 8031–8041.
[166] A.E. Tee, B. Liu, R. Song, J. Li, E. Pasquier, B.B. Cheung, et al., The long noncoding RNA MALAT1 promotes tumor-driven angiogenesis by up-regulating pro-angiogenic gene expression, Oncotarget 7 (2016) 8663–8675.
[167] J.Y. Liu, J. Yao, X.M. Li, Y.C. Song, X.Q. Wang, Y.J. Li, et al., Pathogenic role of lncRNA-MALAT1 in endothelial cell dysfunction in diabetes mellitus, Cell Death Dis. 5 (2014) e1506.
[168] P. Puthanveetil, S. Chen, B. Feng, A. Gautam, S. Chakrabarti, Long non-coding RNA MALAT1 regulates hyperglycaemia induced inflammatory process in the

endothelial cells, J. Cell. Mol. Med. 19 (2015) 1418–1425.
[169] H. Hirata, Y. Hinoda, V. Shahryari, G. Deng, K. Nakajima, Z.L. Tabatabai, et al., Long noncoding RNA MALAT1 promotes aggressive renal cell carcinoma through Ezh2 and interacts with miR-205, Cancer Res. 75 (2015) 1322–1331.
[170] Y. Tang, X. Jin, Y. Xiang, Y. Chen, C.X. Shen, Y.C. Zhang, et al., The lncRNA MALAT1 protects the endothelium against ox-LDL-induced dysfunction via upregulating the expression of the miR-22-3p target genes CXCR2 and AKT, FEBS Lett. 589 (2015) 3189–3196.
[171] E. Leucci, F. Patella, J. Waage, K. Holmstrom, M. Lindow, B. Porse, et al., microRNA-9 targets the long non-coding RNA MALAT1 for degradation in the nucleus, Sci. Rep. 3 (2013) 2535.
[172] Y. Han, Y. Liu, H. Zhang, T. Wang, R. Diao, Z. Jiang, et al., Hsa-miR-125b suppresses bladder cancer development by down-regulating oncogene SIRT7 and oncogenic long non-coding RNA MALAT1, FEBS Lett. 587 (2013) 3875–3882.
[173] J. Liu, Q. Li, K.S. Zhang, B. Hu, X. Niu, S.M. Zhou, et al., Downregulation of the long non-coding RNA Meg3 promotes angiogenesis after ischemic brain injury by activating notch signaling, Mol. Neurobiol. 54 (2017) 8179–8190.
[174] R. Zhan, K. Xu, J. Pan, Q. Xu, S. Xu, J. Shen, Long noncoding RNA MEG3 mediated angiogenesis after cerebral infarction through regulating p53/NOX4 axis, Biochem. Biophys. Res. Commun. 490 (2017) 700–706.
[175] B. Yan, J. Yao, J.Y. Liu, X.M. Li, X.Q. Wang, Y.J. Li, et al., lncRNA-MIAT regulates microvascular dysfunction by functioning as a competing endogenous RNA, Circ. Res. 116 (2015) 1143–1156.
[176] T. Luan, X. Zhang, S. Wang, Y. Song, S. Zhou, J. Lin, et al., Long non-coding RNA MIAT promotes breast cancer progression and functions as ceRNA to regulate DUSP7 expression by sponging miR-155-5p, Oncotarget 8 (2017) 76153–76164.
[177] X. Zhou, W. Zhang, M. Jin, J. Chen, W. Xu, X. Kong, lncRNA MIAT functions as a competing endogenous RNA to upregulate DAPK2 by sponging miR-22-3p in diabetic cardiomyopathy, Cell Death Dis. 8 (2017) e2929.
[178] Z. Lin, J. Ge, Z. Wang, J. Ren, X. Wang, H. Xiong, et al., Let-7e modulates the inflammatory response in vascular endothelial cells through ceRNA crosstalk, Sci. Rep. 7 (2017) 42498.
[179] S. Huang, W. Lu, D. Ge, N. Meng, Y. Li, L. Su, et al., A new microRNA signal pathway regulated by long noncoding RNA TGFB2-OT1 in autophagy and inflammation of vascular endothelial cells, Autophagy 11 (2015) 2172–2183.
[180] S. Blackshaw, S. Harpavat, J. Trimarchi, L. Cai, H. Huang, W.P. Kuo, et al., Genomic analysis of mouse retinal development, PLoS Biol. 2 (2004) E247.
[181] K. Li, Y. Blum, A. Verma, Z. Liu, K. Pramanik, N.R. Leigh, et al., A noncoding antisense RNA in tie-1 locus regulates tie-1 function in vivo, Blood 115 (2010) 133–139.
[182] L. Kurian, A. Aguirre, I. Sancho-Martinez, C. Benner, T. Hishida, T.B. Nguyen, et al., Identification of novel long noncoding RNAs underlying vertebrate cardiovascular development, Circulation 131 (2015) 1278–1290.
[183] K. Li, T. Chowdhury, P. Vakeel, C. Koceja, V. Sampath, R. Ramchandran, Delta-like 4 mRNA is regulated by adjacent natural antisense transcripts, Vasc. Cell. 7 (2015) 3.
[184] M. Boulberdaa, E. Scott, M. Ballantyne, R. Garcia, B. Descamps, G.D. Angelini, et al., A Role for the Long Noncoding RNA SENCR in Commitment and Function of Endothelial Cells, Mol. Ther. 24 (2016) 978–990.
[185] L. Folkersen, T. Kyriakou, A. Goel, J. Peden, A. Malarstig, G. Paulsson-Berne, et al., Relationship between CAD risk genotype in the chromosome 9p21 locus and gene expression. Identification of eight new ANRIL splice variants, PLoS One 4 (2009) e7677.
[186] G. Bochenek, R. Hasler, N.E. El Mokhtari, I.R. Konig, B.G. Loos, S. Jepsen, et al., The large non-coding RNA ANRIL, which is associated with atherosclerosis, periodontitis and several forms of cancer, regulates ADIPOR1, VAMP3 and C11ORF10, Hum. Mol. Genet. 22 (2013) 4516–4527.
[187] O. Harismendy, D. Notani, X. Song, N.G. Rahim, B. Tanasa, N. Heintzman, et al., 9p21 DNA variants associated with coronary artery disease impair interferon-gamma signalling response, Nature 470 (2011) 264–268.
[188] H.M. Broadbent, J.F. Peden, S. Lorkowski, A. Goel, H. Ongen, F. Green, et al., Susceptibility to coronary artery disease and diabetes is encoded by distinct, tightly linked SNPs in the ANRIL locus on chromosome 9p, Hum. Mol. Genet. 17 (2008) 806–814.
[189] A. Helgadottir, G. Thorleifsson, A. Manolescu, S. Gretarsdottir, T. Blondal, A. Jonasdottir, et al., A common variant on chromosome 9p21 affects the risk of myocardial infarction, Science 316 (2007) 1491–1493.
[190] L. Chen, H. Yao, J.Y. Hui, S.H. Ding, Y.L. Fan, Y.H. Pan, et al., Global transcriptomic study of atherosclerosis development in rats, Gene 592 (2016) 43–48.
[191] L. Chen, W. Yang, Y. Guo, W. Chen, P. Zheng, J. Zeng, et al., Exosomal lncRNA GAS5 regulates the apoptosis of macrophages and vascular endothelial cells in atherosclerosis, PLoS One 12 (2017) e0185406.
[192] E.M. Coccia, C. Cicala, A. Charlesworth, C. Ciccarelli, G.B. Rossi, L. Philipson, et al., Regulation and expression of a growth arrest-specific gene (gas5) during growth, differentiation, and development, Mol. Cell. Biol. 12 (1992) 3514–3521.
[193] Y.N. Wang, K. Shan, M.D. Yao, J. Yao, J.J. Wang, X. Li, et al., Long noncoding RNA-GAS5: a novel regulator of hypertension-induced vascular remodeling, Hypertension 68 (2016) 736–748.
[194] Q. Yin, A. Wu, M. Liu, Plasma long non-coding RNA (lncRNA) GAS5 is a new biomarker for coronary artery disease, Med. Sci. Monit. 23 (2017) 6042–6048.
[195] L. Moldovan, K.E. Batte, J. Trgovcich, J. Wisler, C.B. Marsh, M. Piper, Methodological challenges in utilizing miRNAs as circulating biomarkers, J. Cell. Mol. Med. 18 (2014) 371–390.
[196] Q. Liu, Y. Shin, J.S. Kee, K.W. Kim, S.R. Mohamed Rafei, A.P. Perera, et al., Mach-Zehnder interferometer (MZI) point-of-care system for rapid multiplexed detection of microRNAs in human urine specimens, Biosens. Bioelectron. 71 (2015) 365–372.
[197] J. Rice, H. Roberts, J. Burton, J. Pan, V. States, S.N. Rai, et al., Assay reproducibility in clinical studies of plasma miRNA, PLoS One 10 (2015) e0121948.
[198] H. Arata, H. Komatsu, K. Hosokawa, M. Maeda, Rapid and sensitive microRNA detection with laminar flow-assisted dendritic amplification on power-free microfluidic chip, PLoS One 7 (2012) e48329.
[199] Y. Zhao, H. Luo, X. Chen, Y. Xiao, R. Chen, Computational methods to predict long noncoding RNA functions based on co-expression network, Methods Mol. Biol. 1182 (2014) 209–218.