**Non-coding RNAs to Treat Vascular Smooth Muscle Cell Dysfunction**

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**Abbreviations**

AAA - abdominal aortic aneurysm

AD - aortic dissection

Ad-5 - adenovirus serotype 5

ASO - antisense oligonucleotide

AAV - adeno-associated virus

CABG - coronary artery bypass graft

CHD - coronary heart disease

circRNA - circular RNA

CVD - cardiovascular diseases

IA - intracranial aneurysm

LNA - locked nucleic acid

lncRNA - long non-coding RNA

miRNA - microRNA

ncRNA - non-coding RNA

PAH - pulmonary arterial hypertension

PAMAM - Polyamidoamine

PASMC - pulmonary arterial smooth muscle cell

PLL - poly-l-lysine

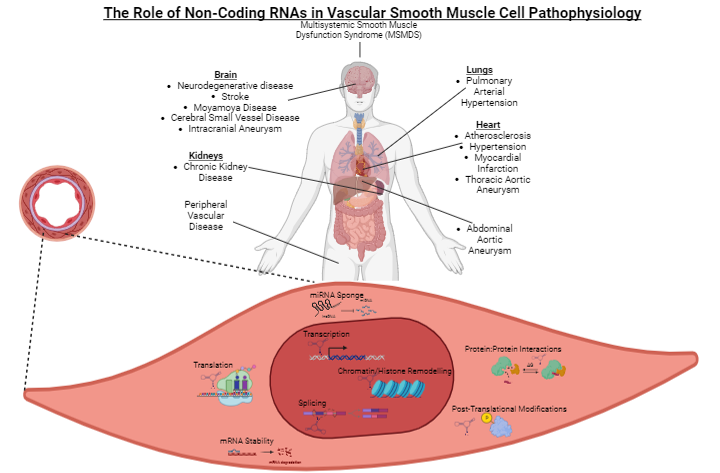
PEI - polyethylenimine

RISC - RNA-induced silencing complex

siRNA - small interfering RNA

TAA - thoracic aortic aneurysm

vSMC - vascular smooth muscle cell



**Abstract**

Vascular smooth muscle cell (vSMC) dysfunction is a critical contributor to cardiovascular diseases, including atherosclerosis, restenosis, and vein graft failure. Recent advances have unveiled a fascinating breadth of non-coding RNAs (ncRNAs) that play a pivotal role in regulating vSMC function. This review aims to provide an in-depth analysis of the mechanisms underlying vSMC dysfunction and the therapeutic potential of various ncRNAs in mitigating this dysfunction, either preventing or reversing it. We explore the intricate interplay of microRNAs, long-non-coding RNAs and circular RNAs, shedding light on their roles in regulating key signalling pathways associated with vSMC dysfunction. Moreover, we discuss the prospects and challenges associated with developing ncRNA based therapies for this prevalent cardiovascular pathology.

1. **Vascular Smooth Muscle Cell Dysfunction in Cardiovascular Diseases.**

Cardiovascular disease (CVD) remains the number one cause of morbidity and mortality worldwide (Tsao et al., 2023), and presents an enormous clinical and economic burden. Older adults demonstrate an increased risk of CVD (North & Sinclair, 2012) and with an increase in the average age of the population, these problems are anticipated to increase, with the annual total cost of CVD in the USA alone predicted to reach $1.1 trillion by 2035 (Dunbar et al., 2018). Whilst great progress has been made in the diagnosis and management of CVD, there remains much to understand as to the underlying molecular mechanisms leading to its pathology. Coronary heart disease (CHD) is the most common type of cardiovascular disease, with 41% of all CVD deaths in the USA attributed to CHD (Tsao et al., 2023). CHD is characterised by atherosclerosis - the progressive build-up of cholesterol and other lipoproteins which can form plaques within the coronary arteries. If left untreated, atherosclerosis will lead to the gradual occlusion of the artery, and to plaque rupture or erosion (Bentzon et al., 2014). In both cases, myocardial infarction, stroke, and death can occur. Vascular smooth muscle cell dysfunction also contributes to several other diseases depending on the affected organ, including kidney disease (Monroy et al., 2015) , and several cerebrovascular disorders (Hayes et al., 2022).

Vascular smooth muscle cells (vSMCs) play a central role in the development of atherosclerosis and plaque formation (Bennett et al., 2016). Although they are primarily composed of lipids, atherosclerotic plaques also contain many different cell types including inflammatory cells (macrophages, dendritic cells, and lymphocytes), and vSMCs, as well as extracellular matrix proteins and other cellular debris. Together, these accumulate to form a cholesterol-rich “necrotic” core. The stability of the plaque is, in part, governed by the thickness of a fibrous cap which forms over the necrotic core, with unstable plaques defined as possessing both a high macrophage/lymphocyte content and a low vSMC content (Yahagi et al., 2016). This definition suggests that vSMCs are positive regulators of plaque stability. This idea has been revisited recently and remains an area of controversy (Grootaert & Bennett, 2021). Multiple studies using lineage-tracing mouse models have demonstrated that vSMCs lose the expression of typical vSMC markers and gain macrophage and foam-like cell expression patterns (Jacobsen et al., 2017; Shankman et al., 2015), while studies in human atherosclerotic plaques have demonstrated that vSMCs transition into foam-like cells upon cholesterol loading (Allahverdian et al., 2014). These foam-like cells express CD68, a widely-used macrophage marker, suggesting that previous studies may have mis-identified atherosclerotic plaque cell types. The role of vSMCs in atherosclerosis progression remains unclear and thus remains an area of much interest and controversy.

In adult blood vessels under healthy physiological conditions, vSMCs function to regulate vascular tone by retaining the capacity to contract with changes in blood flow and blood pressure and display low rates of proliferation (Rzucidlo et al., 2007). However, unlike cardiac and skeletal smooth muscle cells which terminally differentiate, vascular smooth muscle cells possess the ability to rapidly de-differentiate and change phenotype in response to various environmental cues (Owens, 1995). In the mature, healthy blood vessel, vascular smooth muscle cells display a “contractile” phenotype and express vascular smooth muscle cell-specific contractile genes including α-smooth muscle actin, calponin, smooth muscle myosin heavy chain, caldesmon, and metavinculin (Owens, 1995; Sobue et al., 1999). Vascular insults, such as iatrogenic damage, result in a plethora of changes to the vascular environment. Endothelial cells, platelets and leukocytes release a variety of growth factors ( e.g. PDGF-BB, TGF-β1), cytokines (e.g. IL-1, IL-6, and IL-8), chemokines (e.g. MCP-1), metalloproteinases (e.g. MMP-9), and pro-thrombotic mediators (e.g. thrombin) that cooperatively induce vascular smooth muscle cells to de-differentiate and display a “synthetic” phenotype (Owens et al., 2004). This synthetic phenotype is characterised by an increase in proliferation, migration and deposition of extracellular matrix, and decreased expression of contractile genes (Owens et al., 2004; Sobue et al., 1999). Proliferating vascular smooth muscle cells can migrate into the intima of the blood vessel, causing intimal thickening. Neointimal hyperplasia refers to the pathological accumulation of vascular smooth muscle cells and extracellular matrix into the tunica intima layer of the blood vessel as a result of acute injury or chronic haemodynamic changes. Neointimal hyperplasia leads to thickening of the vascular wall and superimposed atherosclerosis, and in the context of surgical intervention, including both venous bypass grafts and fistulas created for dialysis access, leads to reduced surgical success and a recurrence of impaired blood flow in patients (Bonatti et al., 2004). The main causes of neointimal hyperplasia are primarily iatrogenic damage during surgical interventions (coronary artery bypass grafting (accelerated by the introduction of venous tissue into the arterial circulation), balloon angioplasty, vascular stenting, fistula creation, or other percutaneous intervention) aging, and inflammation (de Vries et al., 2016). In the context of coronary artery bypass grafting surgeries, untreated neointimal hyperplasia can lead to complete graft occlusion which can result in myocardial infarction, heart failure and eventual death. Utilising gene and RNA therapies to target and prevent neointimal hyperplasia is a promising strategy, particularly as a means to improve graft patency from coronary artery bypass graft (CABG) surgeries, as access to the grafted vein is available immediately prior to grafting. This proposition has shown great promise in several pre-clinical studies (Cable et al., 1999; George et al., 2011; Mann et al., 1999), however to date no large-scale clinical trials have shown an overall benefit or have been translated into clinical practice (Alexander et al., 2005).

**Non-coding RNA: New Players in Cardiovascular Disease**

Advances in genomic sequencing have led to considerable efforts to accurately annotate the human genome. The relatively recent appreciation that only approximately 1-2% of the human genome encodes proteins has opened new opportunities to understand regulatory RNAs and pathways, particularly towards human disease (Consortium, 2012). In line with this, non-coding RNAs (ncRNAs) have emerged as key regulators of cardiovascular disease and development, acting via epigenetic, transcriptional, and post-transcriptional mechanisms to modulate gene expression. NcRNAs have thus uncovered an important novel outlook on gene regulation in both cardiovascular development and disease, which has the potential to open new opportunities for translational development (Kawaguchi et al., 2023). Amongst various types of CVD, dysfunction of vascular smooth muscle cells is recognised as a central contributor to disease development and progression (Bennett et al., 2016; Zhuge et al., 2020). It is therefore unsurprising that numerous studies have emerged which have identified and characterised non-coding RNAs with a wide variety of roles in vascular smooth muscle cell homeostasis (Ballantyne et al., 2016; Cordes et al., 2009; Han et al., 2021; Mahmoud et al., 2019; Vacante et al., 2021; F. Ye et al., 2020; Zou et al., 2015), and which become mis-expressed in dysfunctional vSMCs. Excitingly, advances in gene-targeting strategies, such as chemically-optimised therapeutic oligonucleotides, open the possibility of targeting these ncRNAs specifically in vascular smooth muscle cells, meaning better therapeutic interventions may be developed which are tailored to a specific molecular pathway, rather than a broader-action phenotype.

Regulatory non-coding RNAs are broadly classified into 2 groups. Group 1 includes small RNAs, classed as RNA species shorter than 200 nucleotides, which include microRNAs (miRNA), ribosomal RNAs (rRNA), transfer RNAs (tRNA), PIWI-interacting RNAs (piRNA), small interfering RNAs (siRNA), small nucleolar RNAs (snoRNA), circular RNAs (circRNA), and other less well-studied short RNAs such as the primate-specific small NFA90-associated RNAs (snaR) (Parrott & Mathews, 2011), Y-RNAs (Tauber et al., 2019) and Vault RNAs (Hahne et al., 2021). Group 2 include long non-coding RNAs (lncRNA), which are greater than 200 nucleotides long. Members of each group have been shown to possess pervasive and wide-ranging functions in vascular smooth muscle cells. In the following sections, we will discuss each of these groups, highlighting important examples which have been characterised and demonstrably shown to drive vascular smooth muscle cell dysfunction, and which have the potential to be targeted for therapeutic intervention in cardiovascular disease. We will then discuss gene targeting methods which have the potential to be applied to modulate the expression of these ncRNA and to treat vascular smooth muscle cell dysfunction.

**2. Small Non-coding RNA Functions in Vascular Smooth Muscle Cells**

The small non-coding RNAs miRNA, siRNA and piRNA are key components of gene silencing in eukaryotes, characterised by their short length (20-30 nucleotides) and their association with members of the Argonaute family of proteins (Kim et al., 2009). MiRNAs, in their mature form (20-24 nucleotides in length), create ribonucleoprotein complexes (miRNPs) by interacting with a member of the Argonaute family of proteins (Suzuki et al., 2015). These miRNPs regulate gene expression through imperfect base-pairing between the miRNA with regions in the 3’ Untranslated Region (UTR) of target mRNA (Bartel, 2009), which induces translational repression or degradation of those mRNA (Bartel, 2004). siRNAs (20-24 nucleotides long) are commonly exogenously administered to induce knockdown of coding or non-coding transcripts, and will be discussed at a later section of the current review. The 3rd type, piRNAs, are a class of small ncRNAs (22-24nt in length) that bind to Argonaute proteins of the Piwi subfamily and have mostly been involved in epigenetic and post transcriptional control of gene expression (Kim et al., 2009). Although they had initially been found to be active in the germline as transposon regulators (Aravin et al., 2008; Cox et al., 1998; Cox et al., 2000), more recent evidence points to functional roles of piRNAs in somatic cells (Ozata et al., 2019).

MiRNAs constitute one of the most thoroughly studied categories of short non-coding RNAs. Currently, 1917 miRNA stem-loops are annotated by the most comprehensive public miRNA repository miRbase, from which 2665 mature miRNA sequences are derived (Kozomara et al., 2019). MiRNAs have been shown to play critical roles in a range of biological processes, including development, proliferation, and apoptosis (Ivey & Srivastava, 2015; Jovanovic & Hengartner, 2006; Liu et al., 2007). Through RNA-sequencing, miRNAs have been shown to possess differential expression patterns across tissues and cell-types, where most sequencing reads corresponded to a relatively small fraction of miRNAs (Akat et al., 2014; He et al., 2012). Each individual miRNA can regulate the expression of multiple target transcripts which can be associated with the same signaling pathway (Kern et al., 2021). This makes miRNAs attractive therapeutic agents, as clinical trials that traditionally target single proteins or nodes in biological pathways often fail to reverse pathogenic phenotypes (Hopkins, 2008; Pammolli et al., 2011). However, due to most protein coding genes encoding multifunctional proteins (Espinosa-Cantú et al., 2020), it is important to expect the possibility of adverse effects that could arise from the pleiotropic nature of miRNA targeting (Li & Rana, 2014). Nevertheless, several pioneering therapeutic strategies have been devised with the aim of modulating the expression of miRNAs intricately linked with disease pathogenesis, and a multitude of clinical trials focusing on either the overexpression or inhibition of therapeutic or pathological miRNAs have shown encouraging results, both in terms of safety and amelioration of disease-associated phenotypes. The diseases addressed in these trials span a wide spectrum, which includes conditions such as Alport Syndrome, Hepatitis C, Fibroplasia and heart failure (Gallant-Behm et al., 2019; Gebert et al., 2014; Gomez et al., 2015; Ruiz-Ortega et al., 2022; Täubel et al., 2021).

Drawing from the potential of miRNAs as therapeutics in a spectrum of diseases, it is particularly crucial to examine their significant roles in vascular physiology and investigate their potential in treating disease caused by vascular dysfunction. New studies on the role of additional miRNA on vascular dysfunction are published regularly, expanding the repertoire of miRNAs with potential therapeutic value in managing and treating vascular pathologies. Some of these studies will be presented in detail below, with additional studies being summarized in Table 1.

Table 1. miRNAs characterised in vSMCs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **miRNA** | **Function** | **Models** | **Targets** | **References** |
| miR-1 | Regulates stem cell differentiation into vSMC, affects vSMC fate and arterial remodelling, modifies SMC proliferation and phenotypic switching. It's involved in regulation of vSMC proliferation, ECM degradation, and hypoxia response in PASMCs. | * *In vitro*: ESC differentiation into SMCs, human vSMCs under regulatable myocardin expression, hypoxia-induced PASMCs * *In vivo*: mouse carotid artery induced neointimal lesions, hypoxia-induced pulmonary hypertension in mice. | Directly interacts with KLF4 during differentiation, Pim-1 in proliferation modulation, SphK1 under hypoxia conditions, and ADAM10 in ECM degradation. | (Chen et al., 2011; Zhineng Fan et al., 2022; Sysol et al., 2018; Xie et al., 2011) |
| miR-15/16 | Implicated in the preservation of contractile vSMC phenotype and the attenuation of smooth muscle de-differentiation and injury-induced neointima formation. | * *In vitro*: represented by the morphological switch of VSMC in response to injury stimuli * *In vivo*: (Rat carotid artery balloon injury model, where it played substantial roles in mitigating smooth muscle de-differentiation and neointima formation | Directly targets YAP, modulating its expression in a manner inverse to miR-15b/16 levels | (Xu et al., 2015) |
| miR-22 | Critical in vSMC phenotypic modulation including vSMC marker gene expression, proliferation, and migration. It also seems to have significant roles in neointima formation following vascular injury and in the apoptosis of vSMC, specifically relevant to aortic dissection | * *In vitro*: vSMCs in a phenotype switching model * *In vivo*: wire-injury mouse model, human femoral arteries from patients with vascular diseases, mouse aortic dissection model | Directly targets and regulates MECP2, HDAC4 and EVI1, implicated in vSMC phenotypic modulation, and p38MAPKα, involved in controlling VSMC apoptosis. | (Yu Xiao et al., 2020; Yang et al., 2018) |
| mir-26a | Inhibits proliferation of rat vSMC and neointimal formation, regulates PDGF-BB-induced vSMC phenotypic switch. | * *In vitro*: PDGF-ββ-stimulated rat vSMC exemplifying regulation of cell proliferation and phenotypic switch * *In vivo*: Rat autogenous jugular vein graft model used to evaluate the role of miR-26a on neointimal formation | Directly targets Smad1, influencing vSMC differentiation marker genes' expression and VSMC phenotypic transition. | (Tan et al., 2017; Yang et al., 2017) |
| miR-29 | It is notable for its role in vSMC differentiation and function, specifically in distal lung vasculature. Also involved in the process of vascular calcification and appears significant in the context of hyperglycaemia-induced changes in vSMCs, thus implicating it in diabetic vascular disease. | * *In vitro*: vSMCs exposed to high phosphate, VSMCs in hyperglycaemic conditions, calcifying rat VSMCs * *In vivo*: distal vasculature of lungs in miR-29 null mice, arteries of rats with chronic renal failure, diabetic mice, and patients with diabetes | Has targets including KLF4, which affects smooth muscle differentiation, ADAMTS-7 which influences vascular calcification and COMP, associated with vascular mineralization. | (Cushing et al., 2015; Du et al., 2012; Hien et al., 2018) |
| miR-33 | Implicated in the attenuation of abdominal aortic aneurysm formation, vascular inflammation, and matrix degradation. It also plays a significant role in neointimal hyperplasia induced by arterial mechanical stretch post-vein grafting, and regulation of venous smooth muscle cell proliferation. | * *In vitro*: Peritoneal macrophages and primary aortic vascular smooth muscle cells from miR-33-/- mice, venous vSMCs exposed to arterial mechanical stretch * *In vivo*: Angiotensin II- and calcium chloride-induced AAA mouse models, bone marrow transplantation experiments, grafted veins using the 'cuff' technique | Interacts with ABCA1, MCP-1, MMP-9, and BMP3, involving pathways like c-Jun N-terminal kinase and p38 mitogen-activated protein kinase. Also, it interacts with SMAD2 and SMAD5, downstream targets of BMP3. | (Huang et al., 2017; Nakao et al., 2017) |
| miR-34 | Modulates expression of key genes in vascular aging and calcification, endothelial cell and vascular smooth muscle cell proliferation and migration. Also, it impacts phenotypic transformation of vSMC and inhibits expression of SIRT1 which mediates cellular functions in cardiovascular diseases. | * *In vitro*: mouse aorta, human umbilical vein endothelial cells, human aortic vSMCs * *In vivo*/*ex vivo*: Mouse models of vascular calcification and human coronary tissues from CAD patients. | Directly impacts SIRT1, PDGFR-β, Axl and has negative correlations with MECP2, HDAC4 and EVI1 | (Badi et al., 2018; X. Li et al., 2020; Hairong Wang et al., 2019) |
| miR-124 | Key role in collagen synthesis in vSMCs and influences plaque stability in atherosclerosis. It also impacts on vSMC proliferation and phenotypic switch, as well as on the stability of plaques in the context of carotid artery stenosis. | * *In vitro*: Aortic root plaques of high-fat-diet fed ApoE-/- mice, vSMC treated with PDGF-BB, human aortic vSMCs * *In vivo*: high-fat-diet fed ApoE-/- mice, carotid artery stenosis patients and healthy individuals | Interacts with P4HA1, SP1 and ITGB1, mediates collagen production | (W. j. Chen et al., 2018; Li & Chen, 2023; Tang et al., 2017; L. Zhang et al., 2017) |
| miR-125b | Regulates osteogenic transformation of vascular smooth muscle cells, vascular calcification and is implicated in aortic aneurysm development. Also, it's involved in controlling proliferation and migration of vSMC, and aortic aneurysm development. | * *In vitro*: Human coronary artery smooth muscle cells undergoing osteogenic transformation, vSMC treated with Ang II and PDGF-BB, providing a model of arteriosclerosis obliterans | Regulates expression or function of SP7, ATP7A, and influences expression of AAMP and SRF. It has the potential to affect inflammatory signalling and might interact with other factors in vascular pathologies, notably NF-κB | (Goettsch et al., 2011; Sudhahar et al., 2019; X. Wang et al., 2021) |
| miR-128 | Regulates vSMC proliferation, migration, and DNA methylation. It promotes apoptosis, lowers inflammation, and despite KLF4 induction, it suppresses vSMC proliferative and migratory characteristics. | * *In vitro*: Assessed in vSMC for proliferation, migration, and DNA methylation studies. Also investigated under atherosclerosis conditions for related markers such as FOXO4 and MMP9 | Interacts with FOXO4, MMP9, Dnmts, Tets, and KLF4. Affects DNA methylation in the Myh11 promoter, suppressing proliferative and migratory characteristics of VSMCs. | (Farina et al., 2020; Qu et al., 2020) |
| miR-132 | Regulates vSMC inflammatory response, neointimal hyperplasia formation, vSMC differentiation, and impedes proliferation and migration of vSMC | * *In vitro*: assayed in vSMC subjected to high glucose conditions and inflammatory stimuli [Kong et al., 2019; Xu et al., 2019]) * *In vivo*: used in mouse model to investigate the effect on cardiovascular diseases stemming from diabetes or atherosclerosis | SIRT1 mRNA (via binding to circ-Sirt1), PTEN (acts as a mediator for cilostazol treatment), E2F transcription factor 5 (under high glucose conditions), leucine-rich repeat (in flightless 1) interacting protein-1 (implicating in vSMC dynamics) | (W.-J. Chen et al., 2018; Choe et al., 2013; Kong et al., 2019; Xu et al., 2019) |
| miR-663 | Regulates vSMC differentiation, inhibits PDGF-induced vSMC proliferation and migration, and attenuates neointimal formation. | * *In vitro*: PDGF-BB activated human aortic vSMC as a representation of vSMC differentiation * *In vivo*: Mouse carotid artery ligation vascular injury model, supports a role in reducing neointimal formation. | JUNB, upregulates vSMC differentiation markers (such as SM22α, αSMA, calponin, and smooth muscle myosin heavy chain). | (Li et al., 2013) |

miRNAs implicated in Vascular Smooth Muscle Cell Dysfunction.

The miR-143/145 cluster has a critical involvement in vSMC phenotypic switching in response to stimuli such as PDGF-BB (Rangrez et al., 2011; Vacante et al., 2019). This cluster, co-transcribed in multipotent cardiac progenitors in mice, is instrumental in guiding the differentiation of multipotent stem cells into vSMCs, with miR-145 specifically required for the myocardin-induced transformation of adult fibroblasts into vSMCs. Additionally, miR-143/145 regulates the proliferative behaviour of these muscle cells by collaboratively targeting a network of transcription factors, including Klf4, myocardin, and Elk-1 (Cordes et al., 2009). Another study showed that serum response factor (SRF) and myocardin precisely regulate the vascular-specific miR-143/145 cluster (Xin et al., 2009). Despite their deletion causing a marked decrease in blood pressure and lack of overt abnormality in smooth muscle differentiation, mice absent of miR-143/145 exhibit significantly impaired neointima formation in response to vascular injury (Xin et al., 2009). This is a consequence of diminished migratory activity and disarray of actin stress fibers in SMCs, reinforcing that miR-143/145 play a crucial part in a SRF-controlled network modulating cytoskeletal remodeling and phenotypic transformation in SMCs during vascular disease (Xin et al., 2009). Consistently with Xin et al., 2009, Boettger et al., (2009) showed that lack of miR-143/145 by genetic knockout in mice promoted the development of neointimal lesions, in addition to resulting in vSMCs remaining in a synthetic state. Through high-throughput proteomics, the authors identified angiotensin-converting enzyme (ACE) as a potential target of miR-143/145, and pharmacological blocking of either ACE or the AT1 receptor partially restored normal vascular function and gene expression in miR-143/145-deficient mice (Boettger et al., 2009). MiR-145 is also downregulated in the vascular walls with neointimal lesion formation and in cultured de-differentiated vSMCs (Cheng et al., 2009). Both *in vitro* and *in vivo*, miR-145 acts as a phenotypic marker and modulator for vSMCs, affecting differentiation marker genes such as SM alpha-actin, calponin, and SM-MHC (Cheng et al., 2009). In the same study, it was also discovered that this modulation occurs through its target gene KLF5 and its downstream signaling molecule, myocardin. Administration of miR-145 in balloon-injured arteries inhibits neointimal growth, suggesting that miR-145 might have therapeutic potential for controlling vascular neointimal lesion formation and other proliferative vascular diseases (Cheng et al., 2009). The cluster is also downregulated in aortic aneurisms versus healthy aortas and is able to decrease neointimal formation *in vivo* when overexpressed (Elia et al., 2009).

The cluster is also implicated in pulmonary arterial hypertension (PAH); upregulation of miR-145-5p was observed in pulmonary artery vSMCs from patients with PAH and genetic ablation or pharmacological inhibition of miR-143 prevented the development of hypoxia-induced PAH (Caruso et al., 2012; Deng et al., 2015). MiR-143/145 is embedded within the locus of the lncRNA CARMN, which also has been identified as a regulator of vSMC pathophysiology. Collectively, it appears that the function of the miR-143/145 cluster in the context of PAH contrasts markedly with its function reported from previous studies in other tissues. Rather than inhibiting aberrant vSMC function, an increase in this miRNA cluster is associated with PAH progression.

MiR-155 has mostly been studied in the immune system, with important regulatory functions within this context (O'Connell et al., 2007; Rodriguez et al., 2007). Recent studies have discovered that miR-155 is also significantly expressed in vSMCs and plays an influential role in their pathophysiology. miR-155 is expressed in and secreted from vSMCs, and it has been shown to be a potent regulator of endothelial barrier function (Zheng et al., 2017). Specifically, miR-155 alters the integrity of endothelial barriers, leading to increased endothelial permeability and enhanced atherosclerotic progression. This suggests that miR-155 could be involved in the communication between different cell types in response to environmental cues (Zheng et al., 2017). A recent study investigated the role of miR-155-5p in the migration of vSMCs under hypertensive conditions (Tong et al., 2023). MiR-155-5p levels were lower in primary vSMCs from spontaneously hypertensive rats and overexpression of miR-155-5p inhibited vSMC migration and oxidative damage while its depletion accelerated these processes. It was further demonstrated that miR-155-5p directly targets the 3'-untranslated region (3'-UTR) of BTB and CNC homology 1 (BACH1), modulating its expression, and that overexpression of miR-155-5p and knockdown of BACH1 synergistically inhibited vSMC migration under hypertensive conditions (Tong et al., 2023). These findings indicate that miR-155-5p may suppress vSMC migration and alleviate vascular remodeling in hypertension by regulating BACH1 expression. In a vascular injury and neointimal formation context specifically, miR-155 has also been identified as a key regulator, where vSMC proliferation and neointimal formation in injured arteries were both reduced by loss of miR-155 (Yang et al., 2015). Notably, the expression of miR-155-target protein, mammalian sterile 20-like kinase 2 (MST2), was increased in the injured arteries of miR-155-deficient mice. miR-155 directly repressed MST2, thereby activating the extracellular signal-regulated kinase (ERK) pathway and promoting inflammatory and oxidative stress responses, which lead to vSMC proliferation and vascular remodeling. The authors concluded that suppressing endogenous miR-155, and thereby upregulating MST2, could be a new therapeutic strategy for vascular injury and remodeling. Wang et al (Wang et al., 2022) discovered a pivotal role for miR-155-5p in PAH. Through *in vitro* experiments, hypoxia treatment promoted pulmonary artery smooth muscle cell (PASMC) proliferation and increased the expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α). They observed an increase in miR-155-5p and a decrease in glycogen phosphorylase L (PYGL) levels in hypoxia-induced PASMCs. Through further experimental work, a direct regulatory relationship was identified between miR-155-5p and PYGL, which is a gene previously identified to be upregulated in hypoxic conditions (Favaro et al., 2012). Elevated miR-155-5p levels in hypoxia-stimulated PASMCs could, therefore, enhance cell proliferation, migration, and cell cycle progression by directly targeting PYGL. From these studies, it is apparent that miR-155 is an integral player in vSMC pathophysiology. miR-155 has shown to have both pathological and protective roles in vascular diseases, making it an intriguing subject for further research and a potentially promising therapeutic target. It would be interesting to specifically interrogate the role of miR-155 in vSMC under pro-inflammatory stimuli and the subsequent changes brought about in immune response. There seems to be a unique interplay due to miR-155's function in both immunoregulation and vSMC biology.

MiR-21 was shown to be upregulated in human, mouse and pig saphenous vein grafts, and pharmacological knockdown of miR-21 expression in organ cultures of human saphenous vein grafts, as well as genetic loss of miR-21 in a mouse *in vivo* model, reduced neointimal formation (McDonald et al., 2013). Further mechanistic studies in rat vSMCs discovered that miR-21 down-regulates c-Ski, a factor previously found to be associated with an increase in vSMC proliferation after arterial injury, by binding to the 3'-untranslated region (UTR) of its mRNA (Li et al., 2014). MiR-21 overexpression repressed c-Ski protein expression and promoted cell proliferation and these effects could be reversed by inhibiting miR-21 or overexpressing c-Ski. The study indicates that c-Ski is negatively regulated by miR-21, elucidating its role in stimulating vSMC proliferation in the progression of arterial injury. Hypoxia induction in pulmonary artery vSMCs (PASMCs) prompted an increase in miR-21 expression which was subsequently shown to be essential for hypoxia-driven cell migration (Sarkar et al., 2010). Moreover, several target genes for miR-21 were identified, including programmed cell death protein 4, Sprouty 2, and peroxisome proliferator-activated receptor-α (Sarkar et al., 2010). These findings underscore the importance of miR-21 in hypoxia-induced pulmonary vascular smooth muscle cell proliferation and migration.

The miR-221/222 cluster, notable for its significant expression in vascular smooth muscle cells (vSMCs), is regulated by PDGF-BB, which is increased following vascular injury. PDGF-BB induces the expression of miR-221 but reduces that of miR-222 in pulmonary artery smooth muscle cells (PASMCs), suggesting differential transcriptional regulation between these two miRNAs under these conditions (B. N. Davis et al., 2009). Induction of miR-221 led to down-regulation of targets c-Kit and p27Kip1. The reduction of p27Kip1 by miR-221 is crucial for PDGF-mediated stimulation of cell proliferation, and the decrease in c-Kit results in suppression of SMC-specific contractile gene transcription by lowering Myocardin (Myocd) expression. MiR-221 and miR-222 additionally exhibited increased expression in rat carotid arteries after angioplasty and in response to growth stimulators in cultured vSMCs (Liu et al., 2009). Knockdown experiments showed miR-221 and miR-222 to be essential to vSMC proliferation, with the p27Kip1 and p57Kip2 genes identified as key players in this process. The results also showed that reduced miR-221 and miR-222 levels suppressed vSMC proliferation and neointimal lesion formation after angioplasty in rat carotid arteries.

The miRNAs mentioned above are among the most researched with respect to vSMC pathophysiology. Additional miRNAs that are implicated in vSMC dysfunction are detailed in Table 1. Considering the evidence indicating the fundamental role of miRNAs in the initiation and progression of a wide array of vascular pathologies, there arises a compelling need to elucidate the full spectrum of their functions within the vasculature. An improved understanding of miRNA functions and the consequences of their manipulation may thus pave the way for innovative therapies that ameliorate disease progression and improve patient outcomes.

1. **Long Non-coding RNA Functions in Vascular Smooth Muscle Cells.**

Long non-coding RNAs (lncRNAs) represent a large, heterogeneous class of biologically active RNA species that have no protein-coding potential (Carninci et al., 2005; Kapranov et al., 2002). lncRNAs have been arbitrarily defined as measuring 200 or more nucleotides in length, and usually display features typical of mRNAs such as RNA polymerase II-dependent transcription, 5’ 7-methyl guanosine (m7G) capping, 3’ polyadenylation and splicing (Mattick et al., 2023), although other lncRNAs have been described that lack these “mRNA-like” features (Wilusz et al., 2008; Wu et al., 2016; Yin et al., 2012). lncRNAs can be intergenic (Ransohoff et al., 2018), intronic (Beckedorff et al., 2013), sense or antisense (Zhang et al., 2014), and can be derived from so-called “pseudogenes” (Rapicavoli et al., 2013). Due to their lack of evolutionary conservation and relatively low levels of expression, lncRNAs were originally suspected to simply be transcriptional noise. However, the last two decades have seen this idea refuted, with a myriad of studies characterising lncRNA with a vast array of functions contributing to cell homeostasis and human disease, often with cell or tissue-enriched expression patterns. Statistics from release 44 (GRCh38.p14) of GENCODE estimates that the human genome contains almost 20,000 lncRNAs, but other studies have suggested there could be closer to 29,000 (Hon et al., 2017) or even more than 100,000 lncRNAs (Uszczynska-Ratajczak et al., 2018; Zhao et al., 2021). Understanding which of these lncRNA have bona-fide functions, and what those functions are, is an important area of future research.

The number of lncRNA that have genuine functions, and which are not simply transcriptional by-products remains a topic of strong debate, with the majority lacking evidence to support any functionality. Several important publications have identified and characterised lncRNA with key functions in vascular smooth muscle cells, and which contribute to atherosclerosis and other cardiovascular pathologies. We will discuss some of these below and a more comprehensive list of lncRNA with defined roles in vascular smooth muscle cells can be found in Table 2.

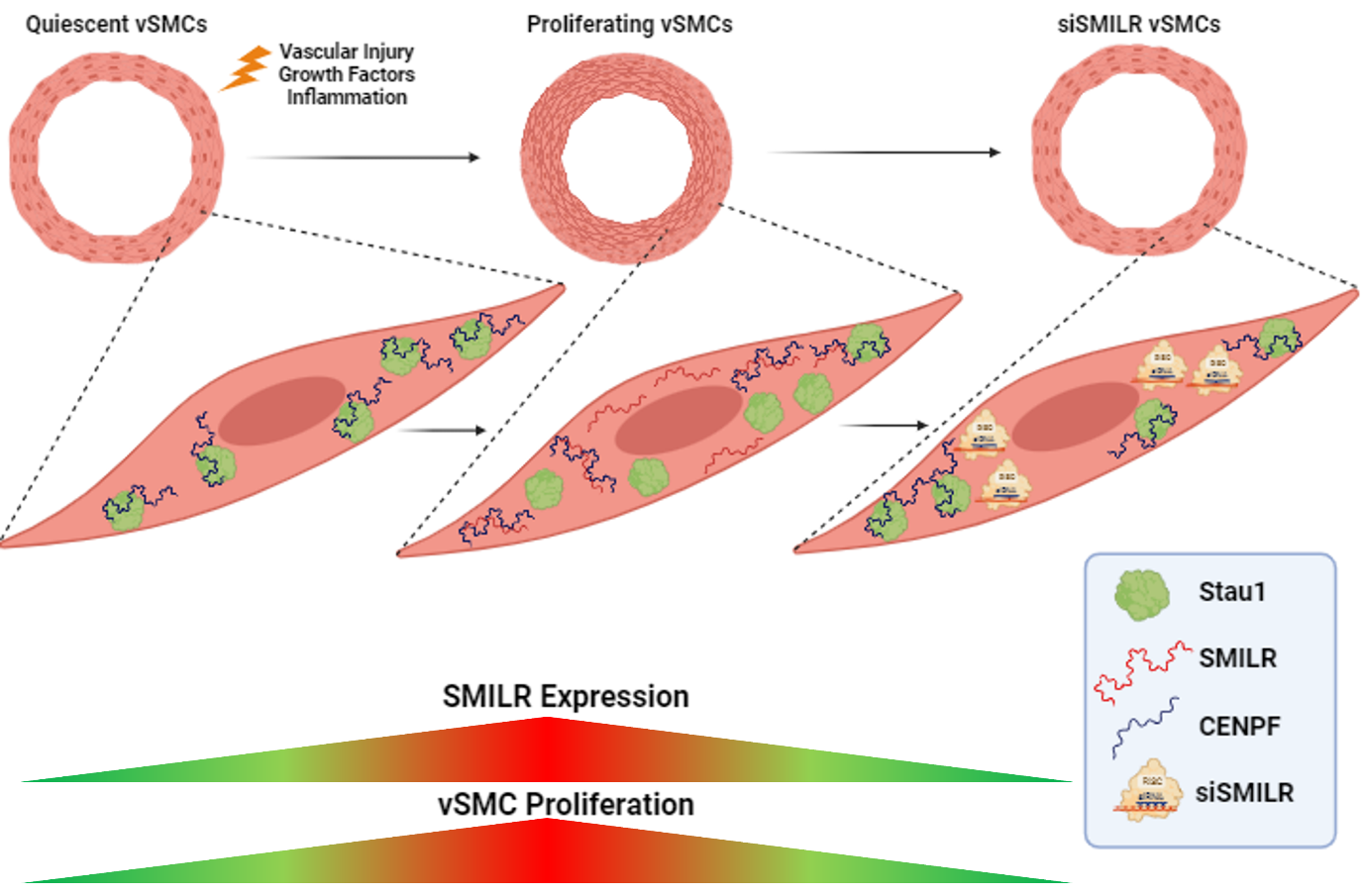
Table 2. lncRNAs characterised in vSMCs.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **lncRNA** | **vSMC Target(s)** | **vSMC Function(s)** | **Disease Model** | **Publication** |
| AC068039.4 | miR-26a-5p | Proliferation, migration | PAH | (Qin et al., 2021) |
| AC105942.1 | hnRNPA2, B1 | Proliferation | Atherosclerosis | (Zhang et al., 2021) |
| AK098656 | MYH11/FN1 | Proliferation | Hypertension | (Jin et al., 2018) |
| AL355711 | ABCG1/MMP3 | Migration | Atherosclerosis | (Kang et al., 2021) |
| ANRIL/CDKN2B-AS1 | AMPK, WDR5, HDAC3, miR-126-5p, miR-143-3p | Proliferation, migration, apoptosis | Atherosclerosis, PAH, IA, Restenosis | (Hu et al., 2022; Huang et al., 2020; J. Li et al., 2021; Ma & Dong, 2021; Tan et al., 2019; S. Wang et al., 2020; C. Zhang et al., 2020) |
| BANCR | miR-34c | Proliferation, apoptosis | Atherosclerosis | (Jiang et al., 2021) |
| C2dat1 | miR-34a | Proliferation, migration | Atherosclerosis | (H. Wang et al., 2019) |
| CARMN | MYOCD | Proliferation, migration | Atherosclerosis | (Dong et al., 2021; Ni et al., 2021; Ounzain et al., 2015; Plaisance et al., 2016; Vacante et al., 2021) |
| CASC2 | miR-532-3p | Proliferation, apoptosis | Atherosclerosis, PAH | (Gong et al., 2019; C. Wang et al., 2020) |
| CRNDE | SMAD3 | Proliferation, migration | Restenosis, AAA | (K. Li et al., 2020; Zhou et al., 2019) |
| CTBP1-AS2 | miR-195-5p | Migration | Atherosclerosis | (Y. Wang et al., 2020) |
| EPS | Wnt/β-catenin | Migration, formation of osteoblast-like cells | Diabetes | (Y. Li et al., 2022) |
| ES3 | miR-95-5p, miR-6776-5p, miR-3620-5p, miR-4747-5p | Formation of osteoblast-like cells | Diabetes | (Zhong et al., 2020) |
| FOXC2-AS1 | miR-1253 | Proliferation, migration | Atherosclerosis | (Y. Q. Wang et al., 2020) |
| GAS5 | miR-21, p53, p300, NOXA | Proliferation, migration | Hypertension, restenosis | (Chen et al., 2021; K. Liu et al., 2019; Tang et al., 2019) |
| GASL1 | TGF-β1 | Proliferation | IA | (Man & Bi, 2019) |
| GIVER | NR4A3, NONO | Oxidative stress, inflammation, proliferation | Hypertension | (Das et al., 2018) |
| H19 | miR-675, miR-599, miR-148b, miR-193b-3p | Proliferation, migration, apoptosis | Atherosclerosis, TAA | (Z. Fan et al., 2022; Lu et al., 2021; Lv et al., 2018; Pan, 2017; Ren et al., 2021; H. Sun et al., 2020; Zhang et al., 2018) |
| HCG18 | FUS | Proliferation, apoptosis | Hypertension | (Y. Lu et al., 2020) |
| HIF1A-AS1 | BRG1 | Proliferation, apoptosis | TAA | (S. Wang et al., 2015) |
| HOTAIR | miRNA-130b-3p/PPARα | Proliferation, apoptosis | Restenosis | (Shen et al., 2022; Xue et al., 2019) |
| Hoxaas3 | H3K9, Hoxa3 | Proliferation | PAH | (H. Zhang et al., 2019) |
| KCNQ1OT1 | miR-221, IκBa | Proliferation, migration, inflammation | CHD | (B. Ye et al., 2020; Zhu et al., 2023) |
| LBX2-AS1 | miR-4685-5p, LBX2 | Proliferation, apoptosis | AAA | (H. Li et al., 2020) |
| LEF-AS1 | miR-544 | Proliferation, migration | Atherosclerosis | (L. Zhang et al., 2019) |
| LINC00281/  Annexin A2 | NF-κB/p65, ANXA2 | Proliferation, migration | Atherosclerosis | (Cheng et al., 2022) |
| LINC00341 | miR-214 | Proliferation, migration | Atherosclerosis | (X. Liu et al., 2019) |
| LINC00473 | miR-212-5p | Proliferation, apoptosis | AAA | (Tian et al., 2020) |
| LINC01123 | miR-1277-5p | Proliferation, migration | Atherosclerosis | (Weng et al., 2021) |
| LINC01278 | miR-500b-5p | Proliferation, migration | AD | (W. Wang et al., 2021) |
| LINC430945 | RhoA | Proliferation, migration | Atherosclerosis | (Cui et al., 2019) |
| LIPCAR | p21, CDK2 | Proliferation, migration | Atherosclerosis | (X. Wang et al., 2019) |
| LOC285194 |  |  | Atherosclerosis | (Cheng et al., 2020) |
| LUCAT1 | miR-199a-5p | Proliferation, apoptosis | AAA | (Xia et al., 2020) |
| MALAT1 | miR-124-3p | Proliferation, apoptosis | Atherosclerosis, TAA, PAH | (Brock et al., 2017; Cheng et al., 2019; Lino Cardenas et al., 2018) |
| MEG3 | miR-361-5p | Proliferation, apoptosis | Atherosclerosis | (M. Wang et al., 2019) |
| MEG8 | miR-181a-5p, miR-195-5p | Proliferation, migration, apoptosis | Atherosclerosis | (Xu et al., 2021; B. Zhang et al., 2019) |
| MIAT | EGR1-ELK1-ERK, miR-641 | Proliferation, migration | Atherosclerosis | (Fasolo et al., 2021; Ma et al., 2021) |
| MRAK048635\_P1 | Rb, E2F | Proliferation, migration, apoptosis | Hypertension | (Fang et al., 2019) |
| MYOSLID | SMAD2, MLK1 | Proliferation, migration | PAH | (J. Zhao et al., 2016) |
| NEAT1 | WDR5, miR-34a-5p, KLF4 | Proliferation, migration | Restenosis, PAH | (Ahmed et al., 2018; Dou et al., 2021) |
| NORAD | miRNA-136-5p | Proliferation, migration | IA | (Lv et al., 2021) |
| NUDT6 | FGF2, CSRP1 | Proliferation, migration, apoptosis | AAA, carotid artery disease | (Winter et al., 2023) |
| p21 | p53, p300,  miR-17-5p | Proliferation, apoptosis | Atherosclerosis | (H. Wang et al., 2021; Wu et al., 2014) |
| PEBP1P2 | CDK9 | Proliferation, migration | Atherosclerosis | (He et al., 2020) |
| PSR | YBX1 | Proliferation | Hypertension | (Yu et al., 2022) |
| PVT1 | miR-27b-3p, miR-3127-5p | Proliferation, migration | AD, AAA | (Huang et al., 2021; S. Li et al., 2021) |
| RNCR3 | KLF2, miR-185-5p | Proliferation, migration | Atherosclerosis | (Shan et al., 2016) |
| RP11-531A24.3 | ANXA2 | Proliferation, migration | Atherosclerosis | (Wu et al., 2021) |
| Rps4l | ILF3 | Proliferation, migration | PAH | (Liu et al., 2020) |
| SAMMSON | miR-130a | Proliferation | IA | (Pan et al., 2021) |
| SENCR | miR-4731-5p, FoxO1, miR-206 | Proliferation, migration | Atherosclerosis, AD | (Bell et al., 2014; Song et al., 2022; F. Ye et al., 2020; Zou et al., 2015) |
| SMILR | CENPF, STAU1 | Proliferation | Atherosclerosis | (Ballantyne et al., 2016; Mahmoud et al., 2019) |
| SNHG12 | miR-7665p, miR-199a-5p | Proliferation, migration | Atherosclerosis | (Liu et al., 2021; Y. Sun et al., 2020) |
| SNHG5 | miR-205-5p | Proliferation, migration, apoptosis | AAA | (Nie et al., 2021) |
| SNHG7-003 | miR-1306-5p | Proliferation, migration | Atherosclerosis | (Zheng et al., 2021) |
| SNHG8 | miR-224-3p | Proliferation, migration | Atherosclerosis | (S. Wang et al., 2021) |
| Sox2ot | miR-145 | Apoptosis, inflammation, oxidative stress | AAA | (Lin et al., 2020) |
| SRA | MEK-ERK-CREB | Proliferation, migration | Atherosclerosis | (C. J. Zhang et al., 2019) |
| TCONS\_00034812 | STOX1 | Proliferation | PAH | (Liu et al., 2018) |
| TUG1 | miR-21 | Proliferation | Atherosclerosis | (Li et al., 2018) |
| UCA1 | miR-582-5p, hnRNP1 | Proliferation, apoptosis | Diabetes, PAH | (Tian et al., 2018; Yang & Han, 2020; Zhu et al., 2019) |
| XIST | miR-539-5p, miR-17 | Proliferation, migration | Atherosclerosis, TAA | (X. Zhang et al., 2020; Zou et al., 2021) |
| ZNF800 | PTEN, AKT/mTOR | Proliferation, migration | Atherosclerosis | (Y. B. Lu et al., 2020) |

lncRNAs as Therapeutic Targets for Vascular Smooth Muscle Cell Dysfunction.

It is unsurprising that efforts to develop therapeutics towards cardiovascular disease have focused on identifying novel factors that drive pathology-associated pathways such as cell proliferation and migration. To identify novel lncRNA that drive vSMC proliferation, Ballantyne *et al*. 2016, induced proliferation in primary saphenous vein-derived vascular smooth muscle cells using a combination of interleukin 1α and platelet-derived growth factor treatment, and subsequently performed deep RNA-sequencing on either proliferating or quiescent vSMCs (Ballantyne et al., 2016). By focusing on novel lncRNA that become expressed specifically in proliferating vSMCs, but not saphenous vein-derived endothelial cells, Ballantyne *et al*., were able to identify more than 300 proliferation-associated lncRNA. Amongst these novel lncRNA was *SMILR* (Smooth Muscle-Induced lncRNA enhances Replication). *SMILR* expression is increased when vSMCs are induced to proliferate and is detected in both the nucleus and cytoplasm. Knockdown of SMILR using siRNA ameliorates interleukin 1α/platelet-derived growth factor-induced proliferation. *SMILR* expression was also increased in regions of unstable atherosclerotic plaques and was detected in plasma from patients with high plasma C-reactive protein, suggesting it could be used as a prognostic biomarker (Ballantyne et al., 2016).

The ability to limit proliferation specifically in vascular smooth muscle cells, and not more broadly across multiple cell types, makes *SMILR* an interesting and important therapeutic target for vascular dysfunction. First-generation drug-eluting stents (DES), such as those coated with Sirolimus or Paclitaxel act to inhibit cell proliferation across multiple vascular cell types by inhibiting mTOR or tubulin, respectively, and have demonstrated improved outcomes relative to bare-metal stents (Moses et al., 2003; Stone et al., 2004a, 2004b). However, subsequent studies demonstrated an increase in the rate of late-stent thrombosis, suggested to occur due to impaired re-endothelialisation and delayed arterial healing caused by globally retarding cell proliferation (Finn et al., 2007; Iakovou et al., 2005; McFadden et al., 2004). These outcomes have been improved with second-generation drug-eluting stents (Joner et al., 2008; Otsuka et al., 2014), however the impact of delaying or impairing re-endothelialisation to any length is still considered a hot topic. Identifying factors that can be targeted to limit proliferation specifically, and only, in vascular smooth muscle cells, such as *SMILR*, is thus an important and beneficial therapeutic approach. Further work aimed at elucidating the molecular mechanism of *SMILR* again utilised deep RNA sequencing from primary saphenous vein derived vSMCs which either over-express *SMILR* via lentivirus, or which have reduced *SMILR* expression as a result of siRNA treatment (Mahmoud et al., 2019). Results from these experiments revealed a SMILR-regulated transcriptional network, which is enriched for genes associated with cell proliferation and mitosis. Pulldown experiments further demonstrated that SMILR binds to both the mRNA of the mitotic CENPF protein, and to the Staufen1 RNA binding protein. Staufen1 has well-defined functions in mRNA nonsense-mediated decay (Gong & Maquat, 2011) suggesting that SMILR competes with Staufen1 for the binding of CENPF, and that this axis regulates vSMC proliferation (Figure 1). This hypothesis is given further support by the observation that depleting SMILR levels using siRNA not only results in a cessation of proliferation in both isolated saphenous vein vascular smooth muscle cells and whole saphenous vein tissue, but also that CENPF levels are reduced after siSMILR treatment (Mahmoud et al. 2019). As discussed previously, excessive proliferation of vascular smooth muscle cells is a fundamental cause of coronary artery bypass graft (CABG) failure. Utilising an siRNA targeted towards SMILR, particularly if administered during graft surgery, could be a promising therapeutic approach to block vSMC proliferation and thus improve graft patency.



**Figure 1. The lncRNA SMILR Drives Proliferation of vSMCs.**

Ballantyne *et al*., (2016) identified SMILR as a lncRNA that drives proliferation specifically in vSMCs. Further work from Mahmoud and Ballantyne *et al*., (2019) demonstrated that as SMILR expression increases in proliferating vSMCs, SMILR binds to the mRNA of the centromeric protein CENPF and protects it from Staufen1-mediated degradation (Stau1), thus promoting the cell cycle and proliferation in vSMCs. Using siRNA to deplete SMILR in proliferating vSMCs results in a cessation of proliferation, mediated through the increased ability of Stau1 to bind CENPF mRNA and target it for degradation.

Cardiac Mesoderm Enhancer-associated Noncoding RNA (*CARMN*) is another well-described and important super-enhancer-associated lncRNA that has the potential to be modulated to treat vascular smooth muscle cell dysfunction. Originally identified in human cardiomyocytes, *CARMN* has a complex relationship with two important developmental miRNA, miR-143 and miR-145, and sits directly upstream from these miRNA (Ounzain et al., 2015). miR-143 and miR-145 have been widely studied and have well-defined functions in cardiac precursor cell specification and differentiation (Cordes et al., 2009; Xu et al., 2009). In particular, miR-143 and miR-145 have been shown to play important roles in the promotion of cardiac precursor cells towards the smooth muscle cell lineage. Several key studies have highlighted the importance of *CARMN* in vascular smooth muscle cell homeostasis, and have demonstrated that its expression becomes decreased in several human and murine vascular disease models (Dong et al., 2021; Vacante et al., 2021). By performing RNA sequencing from atherosclerotic and healthy human coronary arteries, Dong *et* al., demonstrated that the expression of *CARMN* is reduced in dysfunctional vascular smooth muscle cells. This reduction in *CARMN* expression causes vSMCs to lose their contractile phenotype, driven by an attenuated expression of MYH11, TGFB1l1, ACTA2 and CNN1 (as well as miR-145 and miR-143), and increased vSMC proliferation and migration (Dong et al., 2021). To further support the hypothesis that *CARMN* has a critical function in maintaining the vSMC contractile phenotype, Dong *et al*., generated smooth muscle cell-specific *Carmen* inducible knock-out (iKO) mice and performed left carotid artery ligation in these mice and control mice to induce vascular injury. Relative to control mice, *Carmn* iKO mice had exacerbated neointima formation in the injured left carotid artery and had an increase in the number of MKI67-positive proliferating smooth muscle cells in the injured left carotid artery. Collectively, these data demonstrate that loss of *Carmn* expression in SMCs exacerbates neointima formation due to increased vSMC proliferation. To assess the relevance of *CARMN* in human vascular disease, Vacante *et al*., assessed the expression of *CARMN* in atherosclerotic plaques isolated from symptomatic patients undergoing carotid endarterectomy (Vacante et al., 2021). RNA sequencing was performed on stable and unstable regions of human atherosclerotic plaques and analysis from this demonstrated a significant decrease in *CARMN* expression in unstable regions of plaques. To further validate this, *CARMN* expression was evaluated by qRT-PCR on carotid artery stenosis plaques isolated from different patients, which confirmed the downregulation of *CARMN* in advanced versus early atheroma. These important studies highlight that the downregulation of *CARMN* contributes to vascular smooth muscle cell dysfunction and acts to drive vSMCs from the contractile to the synthetic phenotype. Methods to restore *CARMN* expression in patients with vascular disease therefore may be a promising therapeutic approach to impede further vSMC phenotypic switching, and potentially delay the progression of SMC-driven vascular disease.

Perhaps one of the best understood lncRNA, particularly in regard to cardiovascular disease, is *ANRIL* (antisense ncRNA in the INK4 locus), which as its name suggests is located antisense to the INK4 locus. The INK4 locus, located on chromosome 9p21.3, has frequently appeared in genome-wide association studies (GWAS) as harbouring single nucleotide polymorphisms (SNPs) linked to CHD (de los Campos et al., 2010; Gschwendtner et al., 2009; Samani et al., 2007; Schaefer et al., 2009; Schunkert et al., 2011), atherosclerosis (Jarinova et al., 2009), myocardial infarction, both intracranial and aortic aneurysms (Helgadottir et al., 2008), ischemic stroke (Gschwendtner et al., 2009) type II diabetes (Zeggini et al., 2007), and several cancer types (Bishop et al., 2009; Shete et al., 2009; D. Zhang et al., 2017; J. J. Zhao et al., 2016; Zou et al., 2016). *ANRIL* expression itself has been implicated in an increased risk of atherosclerosis (Holdt et al., 2010). Holdt *et al*., (2010) demonstrated an increased expression of two ANRIL transcripts (*EU741058* and *NR\_003529*) in human atherosclerotic plaque samples relative to healthy controls, while also demonstrating that a third ANRIL transcript, *DQ485454*, the most abundantly expressed variant, was unchanged between healthy and diseased tissue, suggesting differential expression of ANRIL transcripts which may harbour different functions (Holdt et al., 2010). Consistent with this hypothesis, loss-of-function studies using siRNA targeting different exons (exon1 and exon 19) of ANRIL demonstrated differential effects on gene expression in human aortic vascular smooth muscle cells, depending on which splicing variant was knocked down. Using a pathway-focused RT-PCR approach, Congrains *et al*., (2012) were able to demonstrate that distinct splice variants of ANRIL regulate the expression of genes involved in atherosclerosis-associated pathways (Congrains et al., 2012).

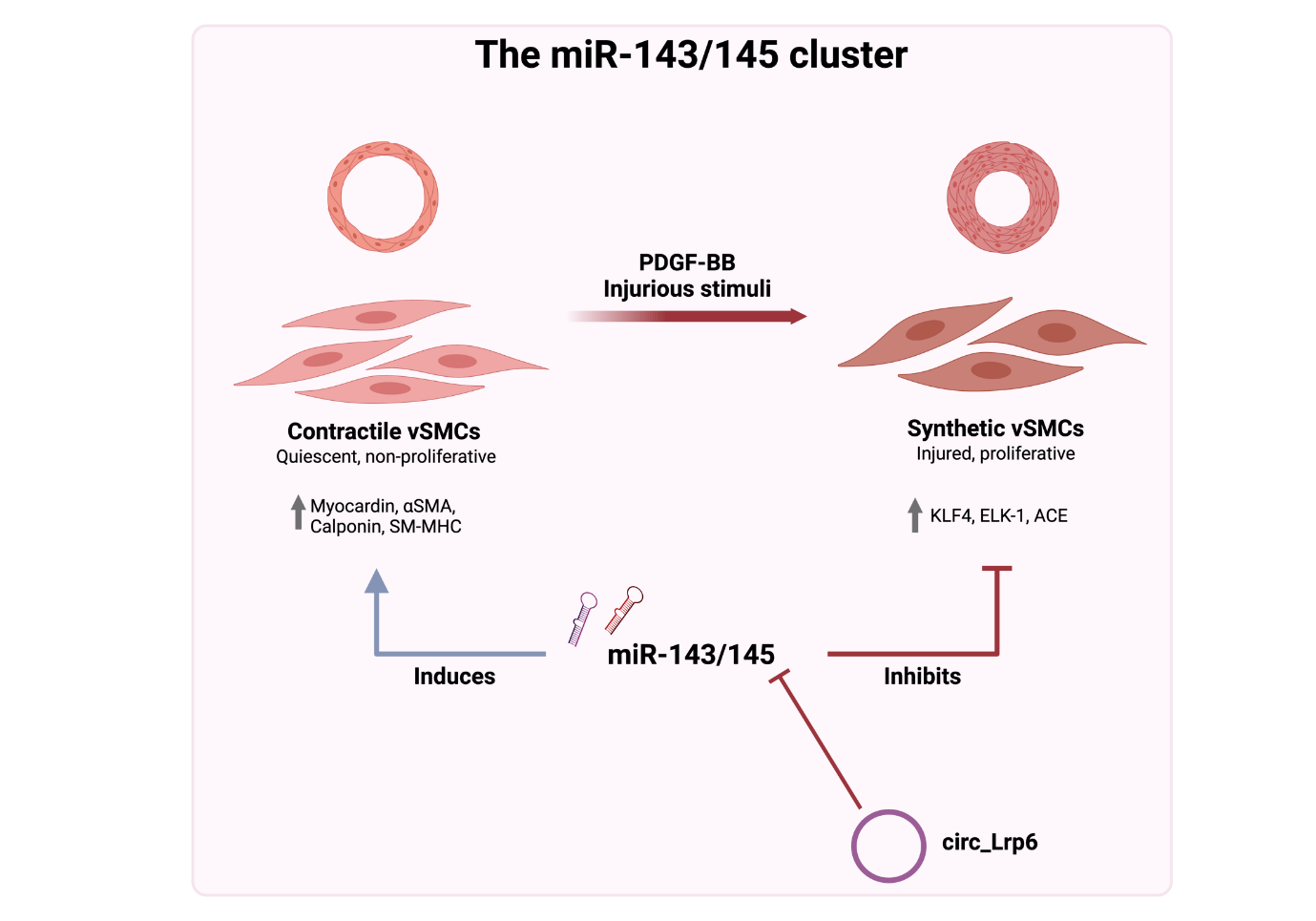
Several papers have demonstrated a mechanistic function for ANRIL in regulating gene expression through binding to components of both polycomb repressive complexes PRC1 (by binding to CBX7) and PRC2 (by binding to SUZ12). Depletion of ANRIL causes a reduction of PRC1 and PRC2 complexes at the INK4 locus, which in turn results in increased expression of two genes within this cluster, p15INK4b and p16INK4a (Kotake et al., 2011; Yap et al., 2010). Specifically in vascular smooth muscle cells, ANRIL has also been shown to have a sponging mechanism towards three microRNAs, miR-339-5p (Huang et al., 2020), miR-7 (Hu et al., 2022) and miR-181a (Tan et al., 2019). Using human aorta vascular smooth muscle cells treated with oxidized Low-Density Lipoprotein (ox-LDL) as a model for atherosclerosis, ANRIL was shown to negatively regulate miR-339-5p, which in turn promotes the expression of fibroblast growth factor receptor substrate 2 (FRS2). This increased expression of FRS2 drives the proliferation and migration of vascular smooth muscle cells, indicating that suppression of ANRIL expression may be a therapeutic strategy to impede vascular smooth muscle cell-associated pathologies (Huang et al., 2020). In further support of ANRIL driving vascular smooth muscle cell proliferation, Hu *et al*., 2022 isolated vascular smooth muscle cells from intracranial aneurysm samples and demonstrated that overexpression of ANRIL promoted cell proliferation and suppressed apoptosis. ANRIL was subsequently shown to bind to and negatively regulate miR-7, which in turn promoted fibroblast growth factor 2 (FGF2) expression and enhanced cell proliferation (Hu et al., 2022). Finally, Tan *et al*., 2019 utilised young and aging vSMCs to investigate whether ANRIL has a role in vSMC cellular senescence. The authors demonstrated that ANRIL expression is reduced in aging vSMCs, and that overexpression of ANRIL could promote cell viability and inhibit vSMC senescence. The authors further showed that these functions of ANRIL were mediated through the negative regulation of miR-181a, which in turn promoted the function of SIRT1 (Tan et al., 2019). SIRT1 is a member of the Sirtuin family of enzymes, which have broad roles in gene expression, cell cycle regulation and apoptosis; primarily acting by deacetylating lysine residues on histones and other proteins (Yamamoto et al., 2007). *ANRIL* expression has been reported to be downregulated in hypoxic human pulmonary artery smooth muscle cells, and further downregulation of *ANRIL* using siRNA was reported to increase both cell proliferation and migration under hypoxic conditions (S. Wang et al., 2020). ANRIL has also been shown to act as a molecular scaffold to regulate chromatin structure and gene expression. Zhang *et al*., (2020) performed RNA pull-down and RNA and protein immunoprecipitation assays in human ox-LDL-induced aortic SMCs and demonstrated that ANRIL binds to both the histone deacetylase HDAC3, and the histone methylation associated protein WDR5. This interaction between HDAC3 and WDR5 is important for regulating the expression of the NADPH oxidase family member NOX1. ANRIL coordinates the localization of WDR5/HDAC3 and regulates the associated epigenetic marks H3K4me3/H3K9ac on the NOX1 promoter (C. Zhang et al., 2020). This suggests that increased ANRIL expression observed in ox-LDL-induced aortic SMCs promote phenotypic switching in these cells. Collectively, these studies demonstrate that ANRIL is an important lncRNA in various vSMC pathological contexts which should be investigated further as a robust therapeutic target.

1. **Circular RNA functions in vSMCs.**

Circular RNAs (circRNAs) are single-stranded RNA loops that lack customary 5ʹ caps and 3ʹ tails, setting them apart from linear RNAs (Huang et al., 2020; Starke et al., 2015). Four distinct circRNA classes exist, each representing a unique synthesis mechanism: exonic (ecircRNAs), circular intronic (ciRNAs), exon-intron (EIcirRNAs), and intergenic circRNAs (Chen & Yang, 2015). Their biogenesis involves a shift from linear splicing to back-splicing, where the 3′ ‘tail’ of an exon is covalently bonded to the 5′ ‘head’ of an upstream exon, creating the circular structure. This process is influenced by the rate of parental gene elongation (Zhang et al., 2016), as well as by its reciprocal regulatory relationship with linear splicing, which compete for access to sequence-specific splice sites and may possibly exert significant influences on the linear splicing of the host mRNA (Ashwal-Fluss et al., 2014). For instance, ecircRNAs predominantly evolve post-back-splicing, sans intronic sequences. Conversely, ciRNAs develop from lariat introns while retaining intron sequences alone. EIcirRNAs can either contain or lack introns due to alternate splicing. Lastly, intergenic circRNAs originate from intervening sequences between two genes via unique splicing (Chen & Yang, 2015). Studies increasingly associate circRNAs with the formation and progression of disease, including vascular smooth muscle cell dysfunction (Ding et al., 2018; Starke et al., 2015). Many were found to be differentially expressed between quiescent and activated vSMCs (Chen et al., 2020). CircRNAs implicated in vSMC function and pathologies have been extensively reviewed recently (Ding et al., 2018; Wu et al., 2022). Below, we provide an updated review of the current literature in the field of circRNAs in vSMCs and highlight open questions which should be answered to improve our understanding of circRNA and their roles in cardiovascular pathology.

Regulating cytoskeletal dynamics in vSMCs is of paramount importance for proliferation, migration, and modifications in the contractile state following injury (Yamin & Morgan, 2012). A central component in these dynamics is the formation of filaments by α-SMA (smooth muscle α-actin), which is encoded by the ACTA2 gene (Sun et al., 2017; Yamin & Morgan, 2012). Sun et al (Sun et al., 2017) unveiled a novel function for circACTA2 in controlling α-SMA expression in vSMCs. They identified a regulatory mechanism involving Neuregulin-1 intracellular domain (NRG-1-ICD), which operates through the NRG-1-ICD/circACTA2/miR-548f-5p axis. Although the authors did not attempt targeting of circACTA2 to ameliorate the injured vSMC phenotype, their study provided a basis for a potential circRNA-based therapeutic target which can be used to fine-tune ACTA2 expression (Sun et al., 2017). Bai et al., (Bai et al., 2023) found that circACTA2 functioned to alleviate vSMC inflammation by curbing the activation of the NLRP3 inflammasome. The mechanism was revealed to be through circACTA2's inhibition of NF-κB p65 and p50 subunits, and its interaction with the p50 subunit. This interaction restricts the formation of a p50/p65 heterodimer and impedes its nuclear translocation triggered by TNF-α, which in turn results in the suppression of NLRP3 gene transcription and inflammasome activation (Bai et al., 2023). Further, circACTA2 was seen to repress vSMC inflammation by mitigating NLRP3 inflammasome-mediated vSMC pyroptosis (Bai et al., 2023). These findings uncovered novel functional roles of circACTA2 in vSMCs and identified the circACTA2–NF-κB–NLRP3 axis as a promising therapeutic target for vascular remodelling.

As previously mentioned, miR-145 is vSMC enriched and important in regulating vSMC identity. More recently, it was discovered that miR-145 interacts with the circ\_Lrp6, a circular RNA isoform of lipoprotein receptor 6 (Lrp6) (Hall et al., 2019). Circ\_Lrp6 functions as an intracellular modulator and a natural sponge for miR-145 that counterbalances the functions of the miRNA in vSMCs. Circ\_Lrp6 possesses multiple miR-145 binding sites, thereby sequestering miR-145 and hindering its regulatory actions on target genes integral to vSMC function. Consequently, circ\_Lrp6 impacts miR-145-mediated regulation of vSMC migration, proliferation, and differentiation (Hall et al., 2019) (Figure 2). The balance between miR-145 and circ\_Lrp6 may play an important role in vascular pathogenesis.



**Figure 2. The functions and regulation of the miR-143/145 cluster in vSMCs**

Diagram depicting the regulation and functions of the miR-143/145 cluster in vSMC phenotypic modulation following PDGF-BB stimulation or injury. The left side illustrates contractile vSMCs, which are quiescent and non-proliferative. The right side shows synthetic vSMCs, which are injured and proliferative. The miR-143/145 cluster maintains the contractile phenotype of vSMCs via inducing the expression of vSMC contractile genes and myocardin, while also targeting KLF4, ELK-1 and ACE, which promote the synthetic phenotype in vSMCs. The inhibitory action of circ\_Lrp6 on the miR-143/145 cluster via sequestering miR-145 is also shown.

CircANRIL is another circRNA involved in vSMC function and vascular disease (Holdt et al., 2016). It is the circularised form of the lncRNA ANRIL located at 9p21. CircANRIL impairs exonuclease-mediated pre-rRNA processing and ribosome biogenesis in human plaque-derived vSMCs by binding to the 60S pre-ribosomal assembly factor Pescadillo Homologue 1 (RES1), which culminates in decreased vSMC proliferation and increased apoptosis via p53 activation (Holdt et al., 2016). All current research on circANRIL in vSMCs is focused on atherosclerosis, and it remains an open question whether this mechanism transcends into injury-mediated vSMC dysfunction in additional vascular disease contexts.

The field of circRNAs in vSMC biology is expanding. Studies to date have largely directed their attention towards validating mechanisms or deciphering phenotypic changes related to circRNA modulation. In advance of these findings, it would be useful to develop a translational perspective, focusing on the *in vivo* modulation of circRNA levels, which itself is a challenge. However, this approach could set the stage for the potential creation of a new class of therapeutic molecules for the treatment of vascular disease.

1. **Modulating ncRNA Expression to Treat vSMC Dysfunction.**

Modulating the expression of ncRNA as a means to treat cardiovascular disease is a promising and realistic goal, particularly with the latest technological advances in the therapeutic oligonucleotide field. Several approaches have been developed, and the choice of which to utilise is dependent on several factors, including sub-cellular localisation (Lennox & Behlke, 2016), and whether the end goal is to up- or down-regulate the ncRNA of interest. We will discuss methods to achieve these goals below.

Down-regulation of ncRNA: Therapeutic Oligonucleotides

RNA-targeting molecules that aim to down-regulate expression generally fall into 4 main categories: i) antisense oligonucleotides (ASOs), ii) small, interfering RNA (siRNA), iii) short, hairpin RNA (shRNA) and iv) aptamers. ASOs, siRNA and shRNA bind to the complementary sequence of their targets via Watson-Crick base pairing with high levels of specificity, meaning they can be designed to target specific RNA with high precision. Additionally, due to their high degree of specificity, ASOs, siRNA and shRNA generally present with fewer off-target effects than other small molecules.

ASOs are single-stranded, synthetic oligonucleotides, generally between 12-30 nucleotides in length, which bind to complementary RNA through Watson-Crick base pairing rules, forming an RNA:DNA hybrid species. Most ASOs act through the recruitment and activation of the endonuclease RNase H1 (Crooke, 1999; Wu et al., 2004), or argonaute2 (Ago2) (Salomon et al., 2015), through which target RNA sequences are cleaved, and the expression of the RNA is thus reduced. Other ASO-like molecules, such as morpholinos (Summerton & Weller, 1997) and peptide nucleic acid molecules (PNAs) (Nielsen et al., 1991) are “occupancy-only” and sterically block the RNA of interest from functioning, being spliced or being translated, although these ASOs are less commonly used (Bennett, 2019; Bennett & Swayze, 2010).

Small interfering RNA (siRNA) and short hairpin RNA (shRNA) represent a similar class of therapeutic oligonucleotide that function based Watson-Crick base pairing and which can be designed to bind to target RNA with high specificity. While their final aim is to block the expression of a target RNA, their mode of action is different from antisense oligonucleotides. Pioneering studies by Fire *et al*., (1998) were the first to demonstrate the existence of RNA interference (RNAi) – an evolutionarily-conserved defence mechanism against the invasion of foreign nucleic acids, and a highly-efficient method to regulate gene expression (Fire et al., 1998). Following this, further studies demonstrated that the introduction of small, interfering RNA to the cell could be used to induce RNAi-mediate gene knockdown, utilising endogenous RNAi machinery within the cell (Elbashir et al., 2001). These discoveries opened an entire field of research which has developed powerful *in silico* siRNA prediction tools and led to the creation of innovative therapies for several diseases. siRNA can be delivered into cells as either single-stranded or double-stranded oligonucleotides of around 20-22 base pairs. Double-stranded siRNA comprise a “sense” or “passenger” strand and an “antisense” or “guide” strand. Once delivered to the cell, siRNAs are incorporated into the RNA-induced silencing complex (RISC) which is comprised of several protein subunits including Argonaute-2 (Ago-2), the endoribonuclease Dicer, protein kinase RNA activator (PACT) and the transactivation response element binding protein (TRBP). The “sense” or “passenger” strand of the siRNA is subsequently cleaved by Dicer, freeing the remaining “guide” strand to direct RISC towards its target RNA, where it binds with high sequence specificity. By bringing RISC to its target RNA, the siRNA effectively mediates cleavage of the RNA by the Ago-2 protein, which is then further degraded by intracellular RNAses (Lee et al., 2006; Liu et al., 2004; Meister et al., 2004; Zhang et al., 2004). After cleavage, the siRNA is able to dissociate from RISC and bind to another RNA molecule. siRNA are thus said to act in a catalytic manner. shRNA function by broadly similar methods as siRNA but are usually introduced into cells as part of a vector-based delivery system rather than directly into the cytosol. shRNAs are also capable of DNA integration and consist of two complementary 19-22 base-pair sequence linked by a shorter, 4-11 nucleotide sequence which forms a hairpin similar to endogenous miRNAs. After transcription, these shRNA are exported to the cytosol where they are cleaved by Dicer to produce siRNA (Brummelkamp et al., 2002).

Aptamers are single-stranded RNA or DNA oligonucleotides which bind to either proteins or small molecules by recognising the tertiary or quaternary structures rather than primary sequence, as in the case for ASOs (Giudice et al., 2020). Aptamers are produced *in vitro* by a process known as SELEX - systematic evolution of ligands by exponential enrichment. Large libraries composed of short oligonucleotides are generated and are amplified by polymerase chain reaction before being incubated with the target of interest. Sequences with poor or no binding to the target of interest are removed, and the remaining aptamers removed from their target binding. Through multiple rounds of this PCR amplification/incubation process, multiple enriched aptamers can be identified, cloned, and sequenced (Gold et al., 2010). To date only one aptamer has entered clinical practice – Macugen (Pegaptanib) – which targets vascular endothelial growth factor (VEGF) and is used to treat age-related macular degeneration (Ruckman et al., 1998).

Clinical Uses of Therapeutic Oligonucleotides

Unmodified oligonucleotides are unstable and are rapidly degraded by endogenous nucleases and thus have limited use therapeutically. To this end, researchers have developed and systematically tested an entire suite of modified oligonucleotides. These range from modifications to the base itself, to the ribose sugar, to the phosphate backbone, and the conjugation of molecules to virtually every available position of a dinucleotide. These modifications are often introduced in combination. For example, a 2’-O-Methyl group can be substituted in place of a 2’-OH group and phosphorothioate linkages can be introduced instead of phosphodiester linkages by the addition of a sulphur atom at one non-bridging oxygen atom within the backbone. Phosphorothioate linkages permit oligonucleotides to have greater resistance to nucleases (Hu et al., 2020). These modifications, as well as many others, have been shown to facilitate better delivery of siRNA *in vivo*, enhanced activity and specificity, suppression of immune activation, and reduced off-target effects, thus enabling efficient and safe gene silencing (Soutschek et al., 2004). Modifications to oligonucleotides have also been essential in the clinical development and adoption of therapeutic siRNA, including Inclisiran (Fitzgerald et al., 2017) and Patisiran (Adams et al., 2018; Coelho et al., 2013). These modifications must be precisely defined and rigorously confirmed by analytical chemistry techniques, as even minor, subtle differences in chemistry can produced radically different pharmacokinetic and biological properties. Readers interested further in the development of these modified oligonucleotides are directed to excellent reviews dedicated to these areas (Crooke et al., 2018; Friedrich & Aigner, 2022; Hu et al., 2020; Ku et al., 2016).

For the targeting of miRNA, bespoke types of ASOs have been developed, each with chemical modifications introduced in their backbone to improve efficacy (Kasina et al., 2023; Lima et al., 2018). These alterations enhance both their stability and specificity (Duygu et al., 2019; Lennox et al., 2013). Antisense oligonucleotidesused to target miRNAs are referred to as anti-miRNA oligonucleotides (AMO) or antimiRs. AntimiRs are single-stranded, typically DNA, and are meticulously designed for complementarity to specific miRNAs, enabling targeted inhibition. Through Watson-Crick binding, antimiRs form duplex structures with their target miRNAs and effectively sequester the mature miRNA. Essential to the success of this method is a higher binding affinity and stability between the miRNA-antimiR complex versus the miRNA-mRNA target complex. To maximise these ratios, several chemical modifications to antimiR backbones have been created. These include Locked Nucleic Acid (LNA) technology (Kauppinen et al., 2005) and antagomiRs (Mattes et al., 2007). LNA belong to high-affinity RNA analogues, unique due to their rigid bicyclic structure. This structure of LNAs mimics the conformation common in RNA, leading to an outstanding hybridization affinity towards corresponding single-stranded RNA sequences (Petersen & Wengel, 2003; Singh et al., 1998). Such a property highlights LNAs' suitability for reproducing RNA structures and facilitating sequence-specific targeting of RNA in both *in vitro* and *in vivo* settings. Essentially, LNAs are oligonucleotides that incorporate at least one LNA monomer with other types of monomers, usually DNA or RNA or 2′-O-Methyl-RNA monomers, forming mixmer LNA oligonucleotides (S. Davis et al., 2009; Esau, 2008). Given the commercial availability of LNA constructs and their compatibility with standard modifications, LNAs have a broad scope of applications, underpinning their significant role in the field of RNA targeting. AntagomiRs represent a chemically modified version of classical antimiRs, which are chemically altered with a phosphorothioate backbone, addition of cholesterol molecule to the 3' end and 2'-O-methylation (Mattes et al., 2007). These modifications improve stability and resistance to degradation by endonucleases, enabling them to inhibit specific miRNAs more effectively by blocking their interaction with target mRNAs. Krutzfeldt et al (Krutzfeldt et al., 2005), using miR-122, showed for the first time that antagomiRs could successfully be used for *in vivo* delivery, and were characterised by a knockdown efficiency that was higher versus other types of chemically modified antimiRs. In a later study, Krutzfeldt et al (Krutzfeldt et al., 2007) further characterised antagomiR-mediated miRNA silencing and showed that miRNA inhibition efficiency was linked to the length of the antagomiR in nucleotides (with 19 nt being optimal for antagomir-122 in hepatocytes) and the dose administered, highlighting the importance of optimising antagomiR design for the system of interest.

There is currently no literature comparing different types of AMOs in vSMCs. However, studies have attempted their use. Most of these studies have not proceeded to clinical trials, with the exception of Foinquinos and colleagues (Foinquinos et al., 2020). They used an LNA antimiR against miR-132 to develop a therapy for heart failure which proceed to phase Ib (Täubel et al., 2021). The study concluded that the novel miR-132 inhibitor used, CDR132L, was safe and well-tolerated by patients, demonstrated linear plasma pharmacokinetics without accumulation, and facilitated a dose-dependent reduction in miR-132 levels. Additionally, the patients administered with CDR132L doses of ≥1 mg/kg showed a median reduction of 23.3% in NT-proBNP, a significant biomarker of heart failure, and experienced noticeable narrowing of the QRS complex (Täubel et al., 2021). Even though the study had a small cohort, these preliminary but positive results warrant further investigation in larger clinical studies. A different study (Y. Xiao et al., 2020) employed the use of antagomiRs in a pre-clinical mouse model to scrutinize the regulatory role of miR-22 in aortic dissection (AD). They observed a decrease in miR-22 and heightened apoptosis of vascular smooth muscle cells (vSMCs) in human AD aorta. More interestingly, downregulating miR-22 in the mouse model notably promoted the progression of AD. *In vitro* experiments revealed that p38 mitogen-activated protein kinase α (p38MAPKα), a target of miR-22, played a crucial role in controlling vSMC apoptosis. Their findings imply that miR-22 may present a potential therapeutic approach for AD by manipulating the apoptosis of vSMCs via the MAPK signaling pathway. Brock and colleagues (Brock et al., 2015) utilized LNA-designed seed blockers in their study of the role of the miR-130 family in hypoxia-induced pulmonary hypertension. The miR-130 family was discovered to have a detrimental effect in this context, which involved repressing the tumor suppressor CDKN1A and ultimately provoking abnormal proliferation of human pulmonary artery vSMC (HPASMC). The innovative use of LNA seed blockers effectively inhibited miR-130 *in vivo*, restoring CDKN1A expression levels and ameliorating the disease phenotype. Notably, this pivotal role of the miR-130 family in the pathogenesis of pulmonary hypertension, and the possibility of therapeutic modulation using LNA molecules, were confirmed using a mouse model of the disease.

LNA–antimiR-21 and a lentivirus-introduced pre-miR-21 has been used to delve into the role of miR-21 in the pathogenesis of abdominal aortic aneurysms (AAAs) in two established murine models (Maegdefessel et al., 2012). As AAA developed in both models (AAA induced by porcine pancreatic elastase or infusion of angiotensin II), an increase in miR-21 expression was observed. A protective effect on aneurysm expansion was noted upon lentiviral overexpression of miR-21, which induced cell proliferation and decreased apoptosis in the aortic wall. A substantial decrease was registered in the expression of the phosphatase and tensin homolog (PTEN) protein after miR-21 overexpression, leading to an increase in the phosphorylation and activation of AKT, and consequently, the emergence of a pro-proliferative and anti-apoptotic pathway. On administering a locked nucleic acid-modified antagomir targeting miR-21 via systemic injection, the pro-proliferative effect of downregulated PTEN was curtailed, resulting in a marked increase in AAA size. These findings were mirrored in mice with nicotine-augmented AAA and human aortic tissue samples derived from patients undergoing surgical AAA repair, with more prominent effects registered in smokers. Conclusively, the modulation of miR-21 expression was proposed as a potential novel therapeutic strategy to limit AAA expansion and curb the progression of vascular disease.

The concept of utilising gene and RNA therapies to treat cardiovascular disease is not new, with studies as far back as 1990 demonstrating that gene transfer to the vasculature is possible (Nabel et al., 1990). However, despite some success in the development of catheter-mediated gene delivery for peripheral vascular disease (Isner et al., 1996; Laitinen et al., 1998) clinical translation of cardiovascular gene and RNA therapies has been slow. Inclisiran (Fitzgerald et al., 2014; Fitzgerald et al., 2017; Frank-Kamenetsky et al., 2008) and Mipomersen (Stein et al., 2012; Visser et al., 2012) are clinically-approved oligonucleotide therapeutics used to lower LDL cholesterol and treat hypercholesterolemia, by targeting the mRNA of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) and Apolipoprotein B, respectively. While utilised to treat a cardiovascular disorder, hypercholesterolemia, both Inclisiran and Mipomersen illicit their functions in the liver. There are currently 16 U.S Food and Drug Administration/European Medicines Agency-approved therapeutic oligonucleotides used in clinical practice (Table 3), which target primarily the liver, but also muscle or central nervous system disorders. Of these approved oligonucleotide therapeutics 14 are RNA-based, however no lncRNA-based therapeutics have entered clinical practice. Given the wealth of studies that are emerging which describe the discovery, functional characterisation and pathological roles of lncRNA, and the diverse functional repertoire these lncRNA possess, often unique to a particular cell type, it is only a matter of time before lncRNA-targeting oligonucleotide therapeutics enter into clinical trials.

Regarding miRNA therapeutics, no FDA- or EU-approved miRNA medicines exist currently, but some are progressing in clinical trials (Gallant-Behm et al., 2019; Gebert et al., 2014; Gomez et al., 2015; Ruiz-Ortega et al., 2022). Miravirsen, an AMO currently tested as an antiviral against Hepatitis C through targeting miR-122, is structurally characterised by the interspersion of LNA ribonucleotides within a DNA phosphorothioate sequence (Gebert et al., 2014). The AMO tested against miR-21 for the treatment of Alport Nephropathy is also chemically modified to possess modified sugar moieties (2′MOE and cEt) to increase their hybridization affinity to miR-21, thereby obstructing its ability to associate with target genes (Gomez et al., 2015). These underscore the promise in using chemically modified AMOs in the clinic for therapeutic inhibition of miRNAs. We are looking forward for that to include treatments against vascular disease in the future.

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| **Proprietary Name** | **Active Compound** | **Category** | **Target Tissue** | **Indication** | **Molecular Target** | **Year Approved** |
| Vitravene | Fomivirsen (Jabs & Griffiths, 2002) | ASO | Eye | Cytomegalovirus Retinitis | CMV IE-2 mRNA | 1998 (discontinued) |
| Macugen | Pegaptanib (Eyetech Study, 2002, 2003; Gragoudas et al., 2004) | Aptamer | Eye | Age-related Macular Degeneration | VEGF165 mRNA | 2004 |
| Kynamro | Mipomersen (Stein et al., 2012; Visser et al., 2012) | ASO | Liver | Homozygous Familial Hypercholesterolemia | Apolipoprotein B mRNA | 2013 (discontinued in Europe) |
| Defitelio | Defibrotide (Baker & Demaris, 2016) | ssDNA | Liver | Hepatic Veno-Occlusive Disease | Multiple - specific mechanism unclear | 2016 |
| Exondys 51 | Eteplirsen (Charleston et al., 2018; Cirak et al., 2011; Kinali et al., 2009; Mendell et al., 2016; Mendell et al., 2013) | ASO | Muscle | Duchenne Muscular Dystrophy | Dystrophin (DMD) pre-mRNA splicing (exon 51 skipping) | 2016 |
| Spinraza | Nusinersen (Chiriboga et al., 2016; Finkel et al., 2016; Hua et al., 2011; Hua et al., 2008; Mercuri et al., 2018) | ASO | CNS | Spinal Muscular Atrophy | Survival of motor neuron 2 (SMN2) pre-mRNA splicing (exon 7 inclusion) | 2016 |
| Onpattro | Patisiran (Adams et al., 2018; Coelho et al., 2013; Suhr et al., 2015) | siRNA | Liver | Heterotrophic Transthyretin Amyloidosis | Transthyretin (TTR) mRNA | 2018 |
| Tegsedi | Inotersen (Ackermann et al., 2016; Benson et al., 2018) | ASO | Liver | Hereditary Transthyretin Amyloidosis, Polyneuropathy | Transthyretin (TTR) mRNA | 2018 |
| Givlaari | Givosiran (Agarwal et al., 2020; Chan et al., 2015; Sardh et al., 2019; Yasuda et al., 2014) | siRNA | Liver | Acute Hepatitc Porphyrias | Delta aminolevulinic acid synthase 1 (ALAS1) mRNA | 2019 |
| Vyondys 53 | Golodirsen (Dzierlega & Yokota, 2020; Frank et al., 2020; Heo, 2020) | ASO | Muscle | Duchenne Muscular Dystrophy | DMD pre-mRNA splicing (exon 53 skipping) | 2019 |
| Waylivra | Volanesorsen (Esan & Wierzbicki, 2020) | ASO | Liver | Familial chylomicronaemia syndrome | Apolipoprotein CIII (APOC3) mRNA | 2019 |
| Viltepso | Viltolarsen (Clemens et al., 2022) | ASO | Muscle | Duchenne Muscular Dystrophy | DMD pre-mRNA splicing (exon 53 skipping) | 2020 |
| Oxlumo | Lumasiran (Garrelfs et al., 2021) | siRNA | Liver | Primary Hyperoxaluria Type 1 | Hydroxyacid oxidase 1 (HAO1) mRNA | 2020 |
| Levqio | Inclisiran (Fitzgerald et al., 2014; Fitzgerald et al., 2017; Frank-Kamenetsky et al., 2008) | siRNA | Liver | Hypercholesterolemia | Proprotein convertase subtilisin/kexin type 9 (PCSK9) mRNA | 2021 |
| Amondys 45 | Casimersen (Shirley, 2021) | ASO | Muscle | Duchenne Muscular Dystrophy | DMD pre-mRNA splicing (exon 45 skipping) | 2021 |
| Amvuttra | Vutrisiran (Adams et al., 2023) | siRNA | Liver | Hereditary Transthyretin Amyloidosis, Polyneuropathy | Transthyretin mRNA | 2022 |

Table 3. FDA/EMA-approved Oligonucleotide Therapeutics.

Up-regulation of miRNAs using miRNA mimics.

MiRNA mimics, which are artificially synthesized double stranded RNAs engineered to mimic the action of naturally occurring miRNAs, consist of a sense strand, perfectly complementary to the antisense miRNA strand. This is different than the endogenous miRNA duplexes where the binding of the sense and antisense strands is imperfect. Chemical modifications in the sense strand of the miRNA mimic are added to achieve inactivation of the passenger strand, leaving only the antisense strand active (Lima et al., 2018; Wang, 2009).

Due to being negatively charged and prone to enzymatic degradation in the blood stream (Y. Wang et al., 2015), naked miRNA mimics are not optimal for therapeutic use *in vivo* and require either chemical modifications that increase stability, or delivery via viral vectors or lipid nanoparticles containing short hairpin RNAs (shRNAs) that correspond to the miRNA mimic duplex of interest (Bofill-De Ros & Gu, 2016). AgomiRs are chemically engineered, cholesterol-conjugated, double-stranded miRNA mimics that are optimized for *in vivo* applications. They function by binding to and regulating target messenger RNAs (mRNAs), mimicking endogenous microRNAs (miRNAs). Employed to either magnify the function of existing miRNAs or implement the role of silenced miRNAs, they serve as aides in gene regulation, contributing to our understanding of miRNA biology and disease pathogenesis. Structurally, agomirs follow the design of a double-stranded miRNA mimic, with one strand fully complementary to the target mRNA and the other strand serving as the guide strand - the active component. However, in comparison to typical miRNA mimics, agomiRs include several modifications like 2'-O-methylation and phosphorothioate linkages for enhanced stability in biological systems, improved target specificity, and resistance to nucleases. They are also conjugated with cholesterol to facilitate cellular uptake (Lima et al., 2018).

The number of studies demonstrating utility of RNA for targeting previously ‘undruggable’ pathways and protein targets involved in development and progression of cardiovascular disease is increasing rapidly (M. Li et al., 2022; Reschke et al., 2022). When a gene needs to be delivered to a target cell inside the human body, it must pass several barriers through the extracellular and intracellular environment (Butt et al., 2022; Sahoo et al., 2021). This is why the delivery of naked genes and nucleic acids is highly unfavourable, and gene delivery requires suitable vectors that can carry the gene cargo to the target site and protect it from biological degradation (Butt et al., 2022). Currently, two types of gene delivery vectors are used in cardiovascular applications, which are viral and non-viral vectors (Butt et al., 2022). The ability of viruses to protect transgenes from biological degradation and their capability to efficiently cross cellular barriers have allowed gene therapy research to develop new approaches utilizing viruses and their different genomes as vectors for gene delivery (Butt et al., 2022). Although viral vectors are very efficient, numerous nonviral systems have been developed that provide sustainable gene expression without triggering unwanted inflammatory and immune reactions, and that are considered nontoxic (Butt et al., 2022).

The most used viruses for vascular therapy development are adenoviruses and adeno-associated viruses (AAV). Adenoviruses are non-enveloped viruses with a double-stranded DNA genome. They are viewed favorably for their adeptness in gene therapy applications due to their significant packaging capacity—in the range of 30-40kb (Gallardo et al., 2021)—which permits the integration of larger therapeutic gene sequences. The adenovirus has been widely used for therapeutic delivery in multiple disease systems, including the vasculature, where its applications have been extensively reviewed (Schwartze et al., 2022). AAVs are small, non-enveloped viruses that house a single-stranded DNA genome (Naso et al., 2017). They represent an attractive vector choice for gene therapy applications, due to their low pathogenicity and an aptitude to mediate long-term gene expression, albeit with a relatively limited packaging capacity, typically around 4.7 kb (Li & Samulski, 2020; Naso et al., 2017; Zhang et al., 2022). Large caveats in the use of viral vectors in a clinical setting include a high chance of neutralisation of the viral vector by the host, as well as sequestration in the liver if administered systemically (Bulcha et al., 2021; Shayakhmetov et al., 2004). For that reason, engineering novel approaches for delivery that are increasingly targeted to the cell type of interest (in our case, to the relevant type of vSMC) or one that uses a localised administration approach as opposed to systemic delivery is imperative. To overcome the limitations of viral vectors, several non-viral delivery systems were designed to protect the nucleic acid therapeutic molecules and to provide increased capacity for target cell entry. Delivery of non-coding RNA therapeutics for cardiovascular disease using non-viral vectors was recently extensively reviewed by (Shah & Giacca, 2022) and (X. Li et al., 2022). Large categories of non-viral methods that have previously been used for ncRNA delivery in the vasculature include cationic polymers, lipid nanoparticles and dendrimers (X. Li et al., 2022; Shah & Giacca, 2022).

1. **Conclusions**

Non-coding RNAs have been identified as key regulators of molecular pathways in vascular smooth muscle cells, and which when perturbed, drive a wide array of cardiovascular pathologies. With the rapid growth of whole transcriptomic analyses in various disease contexts, and indeed at single-cell resolution, there is every reason to expect the number of ncRNA with defined functions in vSMC dysfunction to increase. These studies are of paramount importance if we are to fully understand the signalling pathways involved in the development of cardiovascular disease and crucially, develop new therapies which can be applied clinically to treat these diseases. As opposed to protein-coding genes, which demonstrate wider temporal and tissue expression patterns, ncRNAs often possess cell-specific and occasionally, physiologically-specific expression patterns. This makes ncRNA ideal targets for gene and RNA therapy. Alongside these studies, the continued development of methods by which to deliver ncRNA-modulating compounds will accelerate the translation of these findings into the clinic.

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