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REVIEW
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Emerging Roles of Circular RNAs in Vascular Smooth Muscle Cell Dysfunction

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Atherosclerosis is the major pathophysiological basis of cerebrovascular and cardiovascular diseases. Vascular smooth muscle cells (VSMCs) constitute the main structure of vasculature and play important roles in maintaining vascular tone and blood pressure. Many biological processes and cellular signaling events involved in atherosclerogenesis have been shown to converge on deregulating VSMC functions. However, the molecular mechanisms underlying dysfunctional VSMC in atherosclerosis are still poorly defined. Recent evidence revealed that circular RNAs (circRNAs) are closely related to diseases such as degenerative diseases, tumor, congenital diseases, endocrine diseases and cardiovascular diseases. Several studies demonstrated that circRNAs (e.g., circACTA2, Circ-SATB2, circDiaph3, circ_0020397, circTET3, circCCDC66) played critical roles in the regulation of VSMC proliferation, migration, invasion, and contractile-to-synthetic phenotype transformation by sponging microRNAs (e.g., miR-548f-5p, miR-939, miR-148a-5p, miR-138, miR-351-5p, miR-342-3p). This review describes recent progress in the profiling of circRNAs by transcriptome analysis in VSMCs and their molecular functions in regulating VSMC proliferation and migration.

Keywords: circular RNAs, circRNAs, vascular smooth muscle cells, circ_0002579, circACTA2

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INTRODUCTION

Atherosclerosis is the major pathophysiological basis of cerebrovascular and cardiovascular diseases and can be attributed to the interactions of a myriad of risk factors (Wang et al., 2021a; Qi et al., 2021; Xuan et al., 2021). With the increasing ageing population in most developed countries, the mortality and morbidity of cardiovascular and cerebrovascular diseases are growing worldwide (Birger et al., 2021; Faggiano et al., 2021; Nasir and Cainzos-Achirica, 2021). Vascular smooth muscle cells (VSMCs) constitute the main structure of the vasculature and are key to the maintenance of vascular tone and blood pressure (Zhang et al., 2014; Cil et al., 2021; Zhu et al., 2021). VSMCs are maintained in the non-proliferative stage under the normal condition but can readily proliferate upon vascular injury (Lacolley et al., 2012; Kim and Kang, 2013; Olivieri et al., 2013). Increasing number of studies have indicated that abnormal migration and proliferation of VSMCs are common features of different vascular diseases, such as hypertension, vascular aneurysms, and atherosclerosis. In this regard, VSMCs are known to be heavily involved in atherosclerotic lesion formation (Liu et al., 2011; Yu et al., 2011; Gui et al., 2012; Xu et al., 2021). Many soluble factors and signaling pathways involved in atherosclerogenesis have been shown to deregulate VSMC migration and proliferation as well as transformation from the contractile to the synthetic phenotype (Song et al., 2012; Li et al., 2013; Blumensatt et al., 2014). However, the molecular mechanisms underlying VSMC dysfunctions are still poorly defined due to the complex interactions of VSMCs with their microenvironment and the

heterogeneity of VSMCs (Shanahan and Weissberg, 1998; Kim et al., 2009). Therefore, it is pivotal to shed new light on the relevant cellular and molecular processes to develop mechanism-driven therapeutics for VSMC-related diseases.

Circular RNAs (CircRNAs) belong to a class of newly discovered endogenous regulatory RNAs that are generated by the formation of covalently closed loops that lack 3′-poly-A tails and 5′-caps through back-splicing. In this connection, circRNAs have shown high tissue stability, cross-species conversation, as well as disease stage- and tissue-specificity (Memczak et al., 2013; Ebbesen et al., 2016; Dai et al., 2019; Zhao et al., 2020a; Tu et al., 2020). Growing amount of evidence have demonstrated that most of the circRNAs function as competing endogenous RNAs to regulate gene expression post-transcriptionally *via* sponging microRNAs (miRNAs) (Li et al., 2015; Guo et al., 2020; Li et al., 2020; Ma et al., 2020). Some circRNAs could also bind to proteins directly to mediate their biological functions (Huang et al., 2020). It is noteworthy that, while majority of circRNAs are regarded as regulatory non-coding RNAs, a minor subset, particularly those having internal ribosome entry sites or N^6-methyladenosine modification, could retain the ability to derive protein *via* a process known as rolling circle translation (Abe et al., 2015). Some circRNAs are even be localized in the nucleus to regulate transcription (Bose and Ain, 2018). Functionally, circRNAs are involved in the regulation in most, if not all, biological processes including cell differentiation, autophagy, apoptosis, invasion/migration, metabolism, and proliferation (Liu et al., 2019; Xu et al., 2019; Zheng et al., 2019; Pan et al., 2020; Wang et al., 2021b). It is therefore not surprising that deregulated expression of circRNAs is closely related to different types of diseases, such as degenerative diseases, tumor, congenital diseases, endocrine diseases and cardiovascular diseases (Lukiw, 2013; Li et al., 2019a; Chen et al., 2021a; Li et al., 2021; Papatsirou et al., 2021). With relevance to clinical practice, tissue circRNAs could act as potential biomarkers for prognostication and diagnosis of diseases, particularly tumors (Hu et al., 2019; Liu et al., 2020; Yao et al., 2020; Luo et al., 2021). Recently, several studies demonstrated that aberrant circRNA expression could contribute to the deregulated migration and proliferation of VSMCs (Qin et al., 2021).

In this review, we first summarize circRNA expression profiling studies in VSMCs to provide the scientific community with a comprehensive collection of datasets for selecting specific VSMC-associated circRNAs for further investigation in the future. Specific circRNAs with functional significance and their potential therapeutic exploitation will also be discussed.

CIRCRNA EXPRESSION PROFILING AND INTEGRATIVE ANALYSIS IN VSMCS

Transcriptome-wide RNA sequencing technology has been used to identify the deregulated expression of non-coding regulatory RNAs, including miRNAs, long non-coding RNAs (lncRNAs) and circRNAs, through advanced sample processing workflows and newly developed computational algorithms. For shotgun sequencing-based circRNA profiling, the additional procedures usually include linear RNA removal through exonuclease digestion coupled with identification of back-spliced reads using specific bioinformatic programmes, such as CIRI2 (Gao et al., 2018), DCC (Cheng et al., 2016), Sailfish-cir (Li et al., 2017) and CIRIquant (Zhang et al., 2020), each of which has distinct sensitivity, reliability, and computational requirement. Aside from shotgun sequencing, a newer approach based on rolling circular reverse transcription and nanopore sequencing is available for the annotation of the full repertoires of circRNAs (Liu et al., 2021a). Microarrays with probes that target back-splice sites have also been widely used for circRNA profiling (Li et al., 2019b). In the next step, the identified deregulated circRNAs could be confirmed by RT-qPCR using divergent primers designed to span the circRNA backsplice junction sequence (Panda and Gorospe, 2018). In this respect, attempts have been performed to identify specific differentially expressed circRNAs in VSMCs of different conditions (**Figure 1**; **Tables 1**, **2**).

Platelet-derived growth factor type BB (PDGF-BB) is known to induce VSMC dedifferentiation, migration and proliferation (Lu et al., 2018). Tian et al. used RNA-sequencing to profile circRNA expression of VSMCs exposed to PDGF-BB (Tian et al., 2020). VSMCs were treated without or with PDGF-BB (10 ng/ml). A total of 6,999 circRNAs were annotated, among which 94.06% were exonic, 5.43% were intronic and 0.50% were derived from intergenic regions. A total of 112 circRNAs were differentially expressed between the two VSMCs, with 53 circRNAs downregulated and 59 circRNAs upregulated in the PDGF-BB-treated group. The downregulation of circRNA-5780, circRNA-3875, circRNA-3041 and circRNA-1848 and the upregulation of circRNA-14411, circRNA-13360, circRNA-4452, circRNA-8979 and circRNA-1698 were confirmed using RT-qPCR. Furthermore, they showed that circ_0008776, which harbors 11 miRNA binding sites, had the highest degree of connectivity in the circRNA-miRNA network. In a similar study, Peng et al. used circRNA microarray to identify differentially expressed circRNAs in VSMCs upon exposure to PDGF-BB, in which 169 circRNAs were upregulated whereas 88 circRNAs were downregulated. qRT-PCR confirmed the overexpression of circ_0113656, circ_0001636 and circ_00009732 in the PDGF-BB group compared to control group.

Chen et al. used microarray to profile circRNA expression in quiescent and proliferative VSMCs cultured without or with fetal bovine serum, respectively (Chen et al., 2020). A total of 134 circRNAs were differentially expressed between the two groups, among which 66 circRNAs were upregulated and 68 circRNAs were downregulated in the proliferative group. These 134 circRNAs were divided into three types: 11% circRNAs were intronic, 5% circRNAs were intragenic and 84% circRNAs were exonic. The downregulation of circ_0057072, circ_0007146, circ_0009065, circ_0007888, circ_0006677 and circ_0083756 and the upregulation of circ_0002720, circ_0040705, circ_0009792, circ_0007422, circ_0001304 and circ_0004872 in the proliferative VSMCs were confirmed by RT-qPCR.

Xu et al. performed microarray to study circRNA expression in the balloon-mediated common carotid artery injury model (Hall

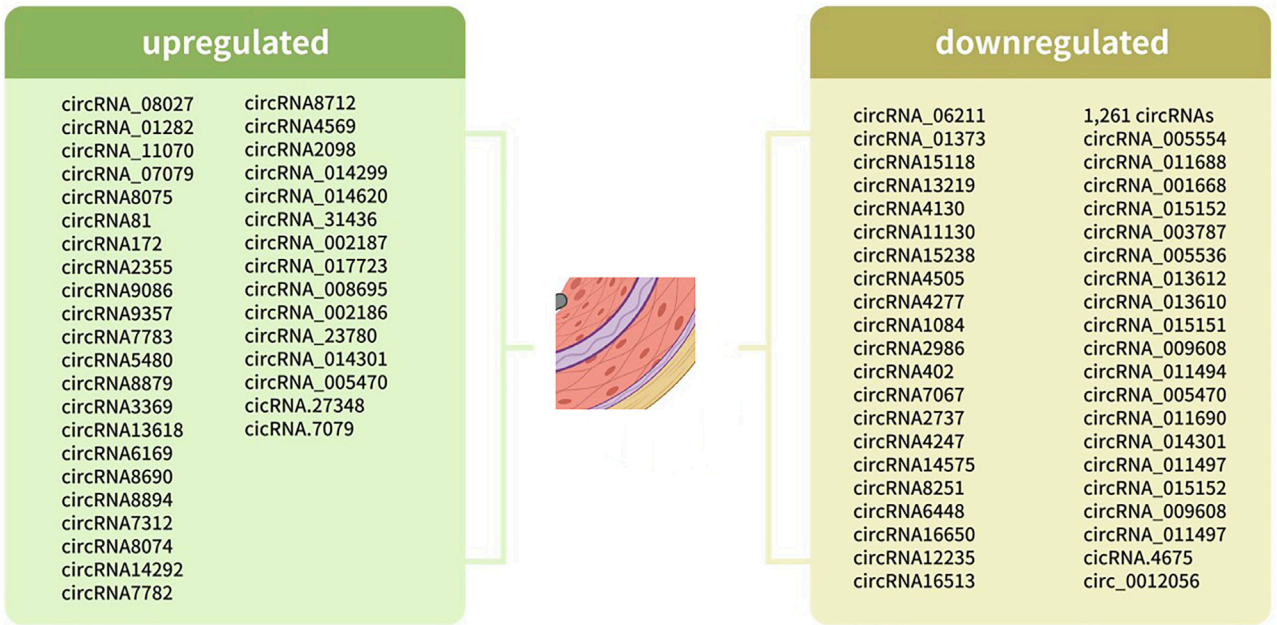

FIGURE 1 | Differentially expressed circRNAs in different status of VSMCs.

TABLE 1 | circRNAs expression profiles in vascular smooth muscle cells.

Num	Method	Sample	Upregulated	Downregulated	References
1	RNA sequencing	PDGF-BB-treated VSMC	59 circRNAs	53 circRNAs	Tian et al. (2020)
2	Microarray	FBS-treated VSMC	66 CircRNAs	68 CircRNAs	Chen et al. (2020)
3	Microarray	Common carotid artery	35 circRNAs	38 circRNAs	Hall et al. (2019)
4	RNA sequencing	Vein graft rat model	54 circRNAs	52 circRNAs	Liu et al. (2021b)
5	Microarray	PDGF-BB-treated VSMC	169 circRNAs	88 circRNAs	Peng et al. (2020)
6	Microarray	Microarray-treated VSMC	44 circRNAs	3 circRNAs	Sun et al. (2020)

TABLE 2 | CircRNAs identified from RNA-sequencing or microarray were confirmed by RT-qPCR in vascular smooth muscle cells.

Num	Method	Sample	Upregulated	Downregulated	References
1	RNA-sequencing RT-PCR	PDGF-BB-treated VSMC	circRNA-14411, circRNA-13360, circRNA-4452, circRNA-8979 circRNA-1698	circRNA-5780, circRNA-3875, circRNA-3041 circRNA-1848	Tian et al. (2020)
2	Microarray RT-PCR	FBS-treated VSMC	circ_0002720, circ_0040705, circ_0009792, circ_0007422, circ_0001304 circ_0004872	circ_0057072, circ_0007146, circ_0009065, circ_0007888, circ_0006677 circ_0083756	Chen et al. (2020)
3	RNA sequencing	Vein graft rat model	circ_0113656, circ_0001636 circ_00009732	—	Liu et al. (2021b)

et al., 2019). A total of 73 circRNAs were found to be differentially expressed, among which 35 circRNAs were upregulated and 38 circRNAs were downregulated in the balloon-injured common carotid artery.

Aberrant VSMC proliferation and migration to the intima contribute to vascular restenosis after the coronary artery bypass graft. Liu et al. utilized whole-transcriptome sequencing to identify differentially expressed circRNAs in an autologous vein graft model in rats (Liu et al., 2021b). 106 out of 2,048 annotated circRNAs were found to be deregulated, among which 54 circRNAs were upregulated and 52 circRNAs were downregulated.

Angiotensin II type 1 receptor (AT_1R) autoantibody (AT_1-AA) could contribute to vascular remodelling. Sun et al. used microarray to depict the circRNA expression landscape in AT_1-AA-treated aortic smooth muscle cells (Sun et al., 2020). A total 47 circRNAs (44 upregulated and three downregulated) were differentially expressed were identified.

Functionally Important circRNAs in VSMCs With Defined Mechanisms of Action

Circ_0002579

Chen et al. found that circ_0002579 was upregulated in the proliferative VSMCs as compared to quiescent VSMCs (Chen et al., 2020). Pathway and gene ontology analyses showed that circ_0002579 was co-expressed with 35 differentially expressed mRNAs that were enriched in the Ras, AMP-activated protein kinase (AMPK) and transforming growth factor (TGF)-β receptor signaling pathways. Circ_0,002,579 was predicted to sponge multiple miRNAs targeting high mobility group AT-hook 2 (HMGA2). Accordingly, knockdown of circ_0002579 downregulated HMGA2 protein level and reduced the expression of a proliferation marker (i.e., PCNA) in VSMCs.

CircACTA2

Sun et al. identified a new circRNA known as circACTA2 that was transcribed from exons five to nine of α-SMA (α-smooth muscle actin) gene. Functionally, circATCA2 sponges miR-548f-5p expression to promote the expression of α-SMA (Sun et al., 2017). Upstream, neuregulin-1 intracellular domain (NRG-1-ICD) was found to induce the expression of circACTA2. These data suggest that the NRG-1-ICD/circACTA2/miR-548f-5p/α-SMA axis may act as a novel treatment target for VSMC dysfunction. In another study, Ma et al. (Ma et al., 2021). demonstrated that circACTA2 was overexpressed in the vascular walls of hypertensive cases and in angiotensin II-induced VSMCs. Knockdown of circACTA2 inhibited angiotensin II-induced VSMC senescence as shown by inhibited expression of p21, enhanced expression of CDK4 and reduction of β-galactosidase-positive VSMCs. RNA immunoprecipitation and oligo pull-down assays demonstrated that both CDK4 mRNA and circACTA2 could bind to ILF3. Angiotensin II enhanced the interaction between circACTA2 and ILF3, thus releasing CDK4 mRNA which degraded rapidly in its unbound form. The authors' data suggested that the ILF3-circACTA2-CDK4 axis may provide a new therapy target for ameliorating VSMC dysfunction in cardiovascular diseases.

Circ-SATB2

Mao et al. demonstrated that STIM1 and circ-SATB2 were overexpressed in the PDGF-BB-induced proliferative VSMCs, while the miR-939 level was downregulated. miR-939 and circ-SATB2 did not influence the level of each other but circ-SATB2 induced STIM1 expression whereas miR-939 suppressed STIM1 expression (Mao et al., 2018). Ectopic expression of circ-SATB2 also decreased SM22-alpha (SM22a) expression while SM22a level was enhanced *via* miR-939. Functionally, both circ-SATB2 and STIM1 induced cell migration and growth of VSMCs whereas overexpression of miR-939 suppressed VSMC migration and growth and induced apoptosis. Mechanistically, the modulatory effects of circ-SATB2 on VSMC apoptosis, migration, proliferation, and phenotypic differentiation were mediated through STIM1.

CircDiaph3

Xu et al. demonstrated that circDiaph3 was localized in the cell cytoplasm of VSMCs (Xu et al., 2019). Knockdown of circDiaph3 suppressed collagen I and cyclin D_1 expression and inhibited VSMC migration and proliferation. Downregulation of circDiaph3 increased Diaph3 expression in VSMCs, in which miR-148a-5p may be one of the targets of circDiaph3. To this end, miR-148a-5p enhanced the expression of markers for contractile smooth muscle cells and suppressed VSMC migration and proliferation. Furthermore, they found that Igf1r was the direct target of miR-148a-5p and Igf1r level was upregulated in the balloon-injured common carotid artery. These data collectively showed that knockdown of circDiaph3 could suppress VSMC proliferation, migration, and dedifferentiation. This circRNA may be a new target for preventing intimal hyperplasia after vascular injury.

Circ_0020397

Wang et al. demonstrated that KDR and circ_0020397 were downregulated while miR-138 expression was upregulated in VSMC and arterial wall samples of intracranial aneurysm (Wang et al., 2019). Ectopic expression of circ_0,20397 induced VSMC growth whereas miR-138 induced VSMC apoptosis. Overexpression of circ_0020397 decreased miR-138 expression in VSMCs where these two non-coding RNAs were negatively correlated with each other. Moreover, KDR was found to be the target gene of miR-138. Overexpression of circ_0020397 induced VSMC growth *via* sponging the miR-138/KDR axis.

CircTET3

Yao et al. demonstrated that circTET3 was upregulated in the grafted vein as compared to the control (Yao et al., 2020). Knockdown of circTET3 suppressed migration of VSMCs where miR-351-5p was identified to be the direct target of circTET3. In contrast, ectopic expression of circTET3 promoted VSMC migration *via* sponging miR-351-5p. Their data suggested that the circTET3-miR-351-5p axis may be a novel potential treatment target for preventing intimal hyperplasia after vein graft.

CircCCDC66

CircCCDC66 was differentially expressed in abdominal aortic aneurysm. Yang et al. showed that depletion of circCCDC66 increased VSMC growth and reduced VSMC apoptosis (Yang et al., 2020). Mechanistically, circCCDC66 enhanced CCDC66 expression *via* sponging miR-342-3p to mediate its effect on VSMC proliferation and apoptosis. Their data suggested that the circCCDC66-miR-342-3p-CCDC66 axis plays a critical role in regulating VSMC function during abdominal aortic aneurysm.

CircCBFB

Yue et al. showed that circCBFB and miR-28-5p were enriched in the Ago2 protein isolated from VSMCs (Yue et al., 2020). Knockdown of circCBFB suppressed GRIA4 and LYPD3 expression, while knockdown of miR-28-5p revered these effects. Functionally, knockdown of circCBFB induced apoptosis of VSMCs, where LYPD3 and GRIA4 were inhibited by miR-28-5p. circCBFB acted as a sponge of miR-28-5p to release LYPD3 and GRIA4 from miR-28-5p-meidated inhibition. These signaling components were needed in circCBFB-regulated VSMC apoptosis. These data suggested that the circCBFB-miR-28-5p-GRIA4/LYPD3 axis is a key regulator of VSMC apoptosis.

Circ_Lrp6

Hall et al. identified a new circRNA, named circ_Lrp6, which was originated from the alternative splicing of lipoprotein receptor 6 (Lrp6), which was highly expressed in the vessels and involved in vascular pathologies (Hall et al., 2019). The authors showed that circ_Lrp6 sponged miR-145 expression as confirmed by luciferase assay and RNA immunoprecipitation. They also found that FASCIN, Yes1, KLF4, ITGβ8 and Lox were targets of miR-145 in VSMCs. Functionally, circ_Lrp6 dampened miR-145-regulated VSMC differentiation, growth, and migration. Knockdown of circ_Lrp6 inhibited intimal hyperplasia in the carotids. These data suggested that circ_Lrp6 is a potential target for preventing aberrant proliferation and migration of VSMCs.

CDR1as

Zhao et al. demonstrated that miR-7 expression was overexpressed, while the CKAP4 and CDR1as were decreased in the aortic samples from patients with abdominal aortic aneurysm as compared to the control group (Zhao et al., 2020b). Ectopic expression of CDR1as or knockdown of miR-7 enhanced VSMC growth whereas downregulation of CDR1as or overexpression of miR-7 produced the opposite effect. CKAP4 was found to be the direct target of miR-7.

CircErbB4

Sun et al. demonstrated that AT_1-AA could induce migration of VSMCs *via* promoting the expression of angiotensin II type 2 receptor (AT_2R). The authors also showed that circErbB4 (also known as circRNA-20314) was overexpressed in the AT_1-AA-exposed mouse aortic smooth muscle cells (Sun et al., 2020). Mechanistically, AT_1-AA increased the expression of circErbB4 and the RNA-binding protein Quaking (QKI) whose knockdown reduced circErbB4 formation. Overexpression of circErbB4 increased AT_2R level whereas circErbB4 knockdown produced the opposite effect. The promoting effect of circErbB4 on AT_2R was mediated through sponging miR-29a-5p. It was thus concluded that the QKI-circErbB4-AT_2R axis plays a crucial role in AT_1-AA-driven VSMC migration during vascular remodeling.

CircDHCR24

Peng et al. reported that circDHCR24 (also known as circ_0113,656) was upregulated in the PDGF-BB-exposed VSMCs (Peng et al., 2020). Knockdown of circDHCR24 suppressed VMSC migration and growth as well as enhancing the expression of two contractile markers (i.e., SM22α and α-SMA) expression but reduced the expression of a synthetic marker (i.e., osteopenia). Mechanistically, circDHCR24 disinhibited MMP9 *via* sponging miR-149-5p.

Circ_0,010,283

Ding et al. showed that HMGB1 and circ_0,010,283 levels were overexpressed in the oxidized low-density lipoprotein (ox-LDL)-exposed VSMCs in which miR-370-3p expression was decreased (Ding et al., 2020). Knockdown of circ_0,010,283 inhibited VSMC migration and growth and attenuated MMP2, MMP9 and cyclin D_1 expression induced by ox-LDL. miR-370-3p was shown to be the target of circ_0,010,283 while HMGB1 was the direct target of miR-370-3p. circ_0010283 modulated HMGB1 expression through sponging miR-370-3p to mediate its effect on VMSC proliferation and migration. Ectopic expression of HMGB1 rescued the miR-370-3p-mediated inhibition of VSMC growth and migration. The authors' data indicated that circ_0010283 promoted VSMC migration and growth *via* the miR-370-3p-HMGB1 axis in the ox-LDL-treated VSMCs.

CircSFMBT2

Luo and Chen showed that circSFMBT2 was upregulated in human neointimal samples obtained by atherectomy as compared to control samples and in PDGF-BB-treated VSMCs (Luo and Huang, 2021). Knockdown of circSFMBT2 suppressed VSMC migration and growth and enhanced the expression of contractile markers, namely, SMMHC, calponin and SM22α. Mechanistically, circSFMBT2 acted as a competing endogenous RNA to bind to miR-331-3p to derepress HDAC5, which decreased the transcription efficiency of Aggf1. These data indicated that circSFMBT2 is an important regulator of VSMC migration and growth *via* modulating the miR-331-3p-HDAC5-Aggf1 axis.

Circ_0020397

Yin et al. showed that circ_0020397 and GREM1 levels were downregulated in VSMCs isolated from patients with intracranial aneurysm (Yin and Liu, 2021). Ectopic expression of circ_0,020,397 or GREM1 induced VSMC proliferation whereas knockdown of circ_0020397 or GREM1 produced the opposite effect. Mechanistically, circ_0,020,397 was found to sponge miR-502-5p to promote GREM1 expression to mediate its promoting effect on VSMC proliferation.

CircUVRAG

Liu et al. used whole-transcriptome sequencing to show that circUVRAG was downregulated in the grafted vein (Liu et al., 2021b). Knockdown of circUVRAG inhibited VSMC migration and adhesion. Interestingly, the UVRAG pre-mRNA was found to be co-localized with NOVA1 in the nucleus while knockdown of NOVA1 inhibited the formation of both circUVRAG expression and linear UVRAG mRNA without altering the level of the UVRAG pre-mRNA. These data suggested that

TABLE 3 | Differentially expressed circRNAs in vascular smooth muscle cells of different phenotypes.

Name	Dysregulation	Sponge target	Phenotype(s) altered by the circRNA	Related gene	Role	References
Circ_0002579	Upregulated	—	Proliferation	HMGA2	Harmful	Chen et al. (2020)
circACTA2	Upregulated	miR-548f-5p	Contractile-to-synthetic phenotype transformation	α-SMA NRG-1-ICD	Harmful	Sun et al. (2017)
circACTA2	Upregulated	—	Senescence	CDK4 ILF3	Harmful	Ma et al. (2021)
Circ-SATB2	Upregulated	miR-939	Migaration apoptosis proliferation Differentiation	STIM1 SM22a	Harmful	Mao et al. (2018)
circDiaph3	Upregulated	miR-148a-5p	Migration Proliferation dedifferentiation	collagen I cyclinD1 Diaph3 Igf1r	Harmful	Xu et al. (2019)
circ_0,020,397	Downregulated	miR-138	Apoptosis proliferation	KDR	Protective	Wang et al. (2019)
circTET3	Upregulated	miR-351-5p	Migration	—	Harmful	Yao et al. (2020)
circCCDC66	Upregulated	miR-342-3p	Apoptosis proliferation	CCDC66	Harmful	Yang et al. (2020)
CircCBFB	Upregulated	miR-28-5p	Apoptosis	GRIA4 LYPD3	Harmful	Yue et al. (2020)
Circ_Lrp6	Upregulated	miR-145	Differentiation Migration proliferation	FASCIN, Yes1 KLF4 ITGβ8 Lox	Harmful	Hall et al. (2019)
CDR1as	Downregulated	miR-7	Proliferation apoptosis	LDH ROS CKAP4	Protective	Zhao et al. (2020b)
circErbB4	Upregulated	miR-29a-5p	Migration	AT2R QKI ADAR1	Harmful	Sun et al. (2020)
circDHCR24	Upregulated	miR-149-5p	Migration Proliferation contractile	MMP9	Harmful	Peng et al. (2020)
circ_0,010,283	Upregulated	miR-370-3p	Migration Proliferation	HMGB1	Harmful	Ding et al. (2020)
CircSFMBT2	Upregulated	miR-331	Migration Proliferation	Aggf1 HDAC5	Harmful	Luo and Huang, (2021)
Circ_0,020,397	Downregulated	miR-502-5p	Proliferation	GREM1	Protective	Yin and Liu, (2021)
circUVRAG	Downregulated	—	Migration adhesion	NOVA1	Protective	Liu et al. (2021b)
circ-ARFIP2	Downregulated	miR-338-3p	Migration, proliferation invasion	KDR	Protective	Qin et al. (2021)
Circ_CHFR	Upregulated	miR-149-5p	linvasion, proliferation migration	NRP2	Harmful	Wang et al. (2021c)

NOVA1 was involved in the modulation of formation of circUVRAG that can suppress VSMC migration and adhesion.

Circ-ARFIP2

Qin et al. showed that circ-ARFIP2 (circ_0,021,001, circRNA ADP ribosylation factor interacting protein 2) and KDR expression were downregulated whereas the miR-338-3p level was upregulated in the arterial wall samples isolated from patients with intracranial aneurysm (Qin et al., 2021). Ectopic expression of circ-ARFIP2 induced VSMCs migration, growth, and invasion partly *via* modulating miR-338-3p. In addition, they found that KDR was a target of miR-338-3p. Overexpression of circ-ARFIP2 enhanced KDR expression. Elevated expression of KDR also increased VSMC migration, growth, and invasion. Silencing of miR-338-3p produced the same effects *via* disinhibiting KDR expression. These data support that circ-ARFIP2 modulated KDR expression *via* sponging miR-338-3p.

Circ_CHFR

Wang et al. demonstrated that circ_CHFR was overexpressed in the PDGF-BB-treated VSMCs where knockdown of circ_CHFR decreased PDGF-BB-induced promotion of cell invasion, growth and migration and inhibition of apoptosis (Wang et al., 2021c). Mechanistically, circ_CHFR targeted miR-149-5p whose suppression attenuated the fucntional effects of circ_CHFR silencing in PDGF-BB-treated VSMCs. Furthermore, the authors showed that circ_CHFR enhanced NRP2 expression through sponging miR-149-5p. Overexpression of miR-149-5p abolished PDGF-BB-induced promotion of cell invasion, growth, and migration *via* regulating NRP2. These data suggested that PDGF-BB upregulated circ_CHFR to modulate the miR-149-5p-NRP2 axis to induce VSMC migration, growth, and invasion. Circ_CHFR may thus serve as a novel potential treatment target for inhibiting aberrant VSMC functions in atherosclerosis.

CONCLUSION

Altered proliferation, migration, and contractile-to-synthetic phenotype transformation of VSMCs underlie the pathogenesis of many vascular diseases, such as hypertension, vascular aneurysms, and atherosclerosis. In this connection, a repertoire of circRNAs of functional significance to VSMCs (**Table 3**) have been identified by whole-transcriptome sequencing or circRNA microarray. These circRNAs mainly act as competing endogenous RNA to sponge miRNAs to derepress the downstream targets. The abovementioned studies also hinted at the potential clinical utility of targeting aberrantly upregulated circRNAs and their derepressed targets for therapeutic purpose. Silencing of these circRNAs with CRISPR/Cas9, antisense oligonucleotides or small interfering RNAs or blocking circRNA-miRNA interactions sterically by morpholinos for clinical translation in human are rapidly developing fields. Nevertheless, how to achieve tissue-specific delivery of these circRNA-targeting therapeutics remains a major technical hurdle. On the other hand, the research on the use of tissue or circulating circRNAs as biomarkers for predicting the progression of cardiovascular and cerebrovascular diseases is scarce. Future efforts should be put forth in this area. Finally, although many differentially expressed circRNAs have been identified by sequencing or microRNAs, the functions and mechanisms of action of only a handful of them have been appropriately studied, particularly in animals. In particular, vascular dysfunction is known to play a crucial regulatory role in tissue aging (Chen et al., 2021b; Chen et al., 2021c). How circRNA deregulation in VSMCs takes part in this process warrants further investigation. It is hopeful that further characterization of VSMC-related circRNAs will enhance our understanding of the pathogenesis of cardiovascular and cerebrovascular diseases and open up novel therapeutic avenue.

AUTHOR CONTRIBUTIONS

ZP, JL, and XHY drafted and wrote the manuscript. ZP, JL, and XHY revised the manuscript. ZP and JL participated in the design of the review. All authors read and approved the final manuscript.

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