

Review

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Review

Vascular Smooth Muscle Cell Dysfunction in Cerebral Small Vessel Disease: Mechanisms and Therapeutic Potential

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Abstract: Cerebral small vessel disease (CSVD) is closely linked to stroke and dementia, marked by structural and functional impairments of small blood vessels in the brain. This review focuses on how vascular smooth muscle cells (SMCs) contribute to CSVD progression. SMCs regulate cerebral blood flow, maintain vascular structure, support glymphatic waste clearance under physiological conditions. However, in CSVD, these cells undergo pathological alterations, such as hypertrophy, degeneration, phenotypic switching, and extracellular matrix abnormalities. These dysregulations are associated with many signaling pathways malfunction or disruptive mechanical cellular responses. Emerging treatments, such as drugs targeting cyclic nucleotide pathways, show promise in improving blood flow and vascular stability. Despite progress, the molecular mechanisms under SMCs dysfunction in CSVD remain incompletely understood. A deeper exploration of SMCs biology, coupled with clinical translation of preclinical findings, is critical for developing effective therapies to alleviate the growing burden of CSVD.

Keywords: cerebral small vessel disease; smooth muscle cells; pathological alterations; Therapeutic potential; vascular remodeling

1. Introduction

Cerebral small vessel disease (CSVD) presents with diverse clinical symptoms. Patients may exhibit either acute stroke or chronic progressive symptoms, including mood disorders, gait instability, dysphagia, abnormal urination, and cognitive decline [1]. Its neuroimaging features stem from structural changes in the cerebral microvasculature, involving arteries, arterioles, capillaries, and venules [2]. Neuroimaging criteria defined by the STRIVE-2, including white matter hyperintensities, lacunar infarcts (vascular origin), recent small subcortical infarcts, enlarged perivascular spaces, cerebral microbleeds, cortical superficial siderosis, and brain atrophy [3].

CSVD can be classified into two types: sporadic and hereditary. Sporadic cases are strongly associated with modifiable risk factors like hypertension, diabetes, and smoking [4]. Hereditary subtypes include cerebral amyloid angiopathy and non-amyloid genetic diseases. Non-cerebral amyloid angiopathy includes immunologically mediated or monogenic small vessel diseases [5]. The latter is most prevalently represented by cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL), which is caused by pathogenic mutations in the NOTCH3 gene [6].

Vascular smooth muscle cells (SMCs), located in the intima-media (middle layer) of vessels, are the largest number of cells in the arteries [7]. Being continuously exposed to the mechanical and biochemical signals generated in the blood compartment, SMCs are involved in all physiological functions and pathological variations occurring in the vascular wall [8]. In addition to maintaining the structural integrity of blood vessels, these cells play a crucial role in vascular function via

vasodilation, vasoconstriction, phenotype alteration, and the synthesis of the vascular extracellular matrix. Given the diversity of their roles, SMCs are not terminally differentiated and display phenotypic plasticity. Figure 1 is drawn based on the arterial structure and cellular phenotypes, with references from Lorigo, et al. [9].

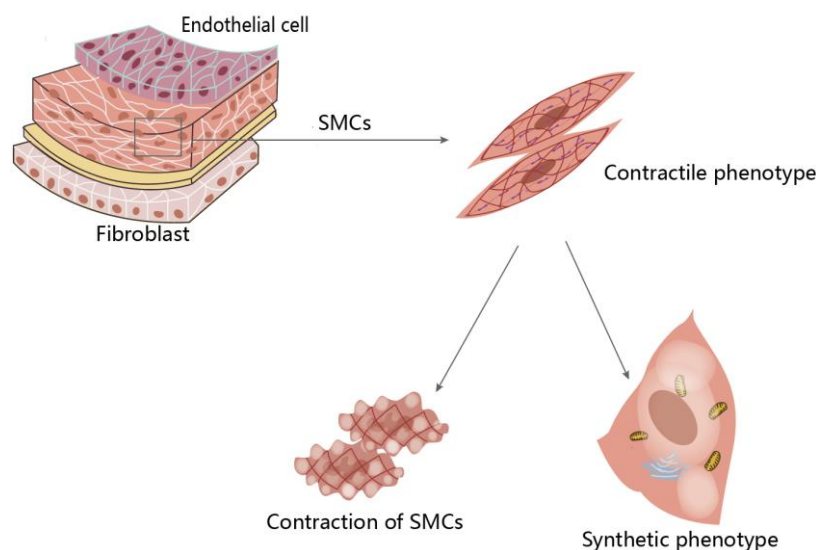


Figure 1. Vascular structure and phenotypes of SMCs. SMCs are located in the intima-media, the middle layer of blood vessels, and are the most abundant cells in arteries. These cells are not terminally differentiated and have phenotypic plasticity. SMCs achieve this through vasodilation, vasoconstriction, phenotype changes, and synthesizing the vascular extracellular matrix. Figure was drawn referencing Lorigo, et al. 2021.

SMCs are key regulators of cerebral blood flow (CBF) [10], glymphatic clearance [11], and vascular remodeling [12], and these functions are pivotal in the progression of CSVD. Basic research indicates that SMCs can undergo various pathological changes, including hypertrophy, proliferation, degeneration, loss, and phenotypic alterations in different types of CSVD. Moreover, numerous signaling molecules impact the function, phenotype, and morphology of SMCs. In this brief review, we aim to summarize the SMCs related physiological functions, pathological changes, blood flow regulation disorders, and molecular signals in the context of CSVD.

2. The Function of SMCs in Physiological Conditions

2.1. Blood Pressure Sensing and Blood Flow Adjustment

As primary sensors of blood pressure fluctuations, SMCs in arteries and arterioles dynamically regulate CBF through mechanosensory signal transduction. When exposed to mechanical stress, these cells undergo transient membrane depolarization, a process critical for maintaining vascular resistance [13]. This electromechanical coupling directly modulates vascular diameter: luminal constriction occurs with elevated blood pressure, while dilation accompanies pressure reduction, thereby establishing an intrinsic CBF regulatory mechanism. Notably, SMCs in penetrating and pre-capillary arterioles serve as key effectors in this autoregulatory cascade. Mechanistic studies reveal that regulatory process involves coordinated activation of membrane ionic channels [14], G-protein coupled receptor [15], and downstream pathways such as Rho kinase [16,17].

2.2. Providing Impetus for Glymphatic Clearance

The glymphatic system in the brain responsible for the dynamic flow and substance exchange between cerebrospinal fluid (CSF) and brain interstitial fluid [18]. This system functions similarly to the peripheral lymphatic system in clearing fluids and metabolic waste [19]. The circulation path

starts with CSF entering the perivascular spaces around arterioles from the subarachnoid space. It then moves through the periarteriolar space into the cerebral parenchyma, subsequently mixing with the interstitial fluid within the parenchyma. Eventually, it exits through the perivascular spaces around veins and is finally absorbed into the venous sinuses via arachnoid granulations in the dura mater [20]. Figure 2 built upon a diagram of glymphatic system adapted from Tian, et al [21]. Crucially, this process is driven by rhythmic vascular diameter changes originating from cardiac-driven hemodynamic pulsations. SMCs stand out as central regulators of glymphatic clearance through modulating vascular pulsatility. Arteriolar SMCs transduce cardiac impulses into biomechanical waves along pial and penetrating arteries, transmitting pulsatile energy from central vessels to distal periarteriolar spaces [22]. However, we cautiously speculate that SMCs function not merely as passive relay, but as active mitigators by dynamically adjusting vascular tone which converts vascular pulsations into precisely regulated hydrodynamic force, thereby playing a role in glymphatic clearance.

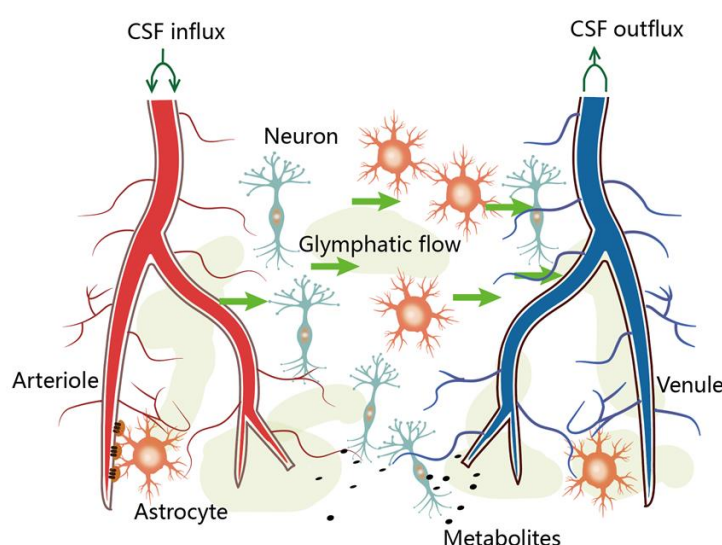


Figure 2. Schematic diagram of the glymphatic system. The glymphatic system regulates the flow and exchange between cerebrospinal fluid and brain interstitial fluid. This system operates through a structured pathway: CSF initially enters the brain's perivascular spaces surrounding arterioles from the subarachnoid space. It then flows through these periarteriolar space into the cerebral parenchyma, where it mixes with interstitial fluid to facilitate waste clearance. Finally, the fluid exits via perivenous spaces around veins and is absorbed into the venous sinuses through arachnoid granulations in the dura mater. This figure was adapted from Tian, et al. 2022.

2.3. Participating in Vascular Remodeling

In response to vascular injury, mature SMCs markedly increase their rates of proliferation, migration, and synthesis, which results in alterations in morphology, structure, and function. This process is known as plasticity of SMCs and displays as phenotypic changes [17]. Specifically, SMCs can shift from classic contraction phenotypes to synthesis, fibroblasts, and even macrophage-like phenotypes in response to changes in the internal environment [23,24]. Plasticity of SMCs allows the vascular system to remodel during vascular development, and enables vascularized tissues to repair and regenerate when faced with injury [25]. During atherogenesis, SMCs migrate from the media layer of healthy arteries to the intima and form a protective fibrous cap. However, as the plaque progresses, phenotypic switching occurs and secretes collagens which stabilize plaque [26].

3. Pathological Transformations of SMCs in the Progression of CSVD

3.1. Hypertrophy and Proliferation

Small cerebral vessels undergo structural modifications induced by persistent high blood pressure in the early stages of CSVD, leading to reduced lumen diameter, vascular stiffening, and increased vascular resistance. These alterations are partly due to hypertrophic remodeling of SMCs, just as demonstrated by promoted expression of alpha-smooth muscle actin (α -SMA), collagen I, and collagen IV in hypertensive rat models [27]. In addition, SMCs proliferation and the production of fibronectin and type IV collagen are promoted by Fabry disease, a hereditary form of CSVD that affects vascular endothelial cells and vascular SMCs across various organs, including the brain, heart, and kidneys [28].

3.2. Loss and Degeneration

The loss and degeneration of arterial SMCs are especially prominent in inherited CSVD. The loss and reduction of SMCs in cerebral arterioles walls are particularly severe in patients with CADASIL and cerebral autosomal recessive arteriopathy with sub-cortical infarcts and leukoencephalopathy (CARASIL) [29-31]. These two forms of CSVD are caused by single-gene mutations: CADASIL (caused by mutations in the NOTCH3 gene) and CARASIL (caused by mutations in the HTRA1 gene). Another hereditary form of CSVD attributed to mutations in the COL4A1 or COL4A2 gene, which are associated with spontaneous intracerebral hemorrhages (ICHs) [32]. Arterial SMCs loss is significantly shown in patients and mice with COL4A1 gene mutations [33,34]. Diminished coverage of SMCs in ruptured arteries, as revealed by pathological analyses, is the original cause of these ICHs [33,35].

3.3. Phenotype Remodeling and Changes of Vascular Extracellular Matrix

Phenotypic switching of SMCs refers to the process by which SMCs change from one phenotype to another in response to various stimuli [36]. In mature arteries, SMCs typically maintain a contractile phenotype characterized by low synthetic activity. However, in response to local extracellular signals, SMCs can transition to a synthetic phenotype marked by producing extracellular matrix (ECM) and proliferation. This phenotypic conversion is also a pathological feature observed in vascular remodeling associated with CSVD. In the spontaneously hypertensive rat (SHR) model of CSVD, SMCs shift from a contractile to a synthetic phenotype during chronic hypertension and aging [37]. This phenomenon is also evidenced in mice models of CSVD by the low expression of the contractile marker α -SMA and high expression of the synthetic marker proliferating cell nuclear antigen (PCNA), indicating SMCs phenotypic conversion [38].

The ECM includes components such as collagen, elastin, hyaluronic acid, and laminin. These molecules form a complex network providing mechanical support to cells in vessel and maintaining viscoelasticity to blood vessels, enabling arteries to expand and contract during the cardiac cycle [39]. Synthetic phenotype derives from phenotype remodeling are capable of producing the ECM. In CSVD, pathological changes can manifest as a disorder in the composition of ECM in the blood vessel wall. Reduced elastin levels have been observed in SHR stroke-prone rats [40], and increased deposition of collagens in the media of vascular wall has been reported in arteries from hypertensive individuals [41] and animal models of hypertension [42,43]. Pathological changes in the vascular ECM are notable in CADASIL, with abnormal accumulation of NOTCH3 protein and other ECM proteins accumulate around SMCs in the brain microvasculature [44]. Additionally, impairment of folding and secretion of collagen IV into the basement membrane can be observed in individuals with mutations in the COL4A1 and COL4A2 genes [45].

3.4. Impairment of Glymphatic Clearance

Declination in glymphatic clearance also contributes to the pathological process of CSVD, due to the accumulation of abnormal proteins and metabolites in brain tissues [21,46-49]. SHR are routinely used in CSVD animal research, and clearance capacity of glymphatic system in SHR is lower compared to normal rats [50]. Currently, various non-invasive magnetic resonance imaging techniques have been developed to quantitatively study glymphatic clearance capacity, such as the DTI-ALPS technique [51,52]. Imaging studies have demonstrated that patients with CSVD have reduced clearance function when compared with normal control populations, and glymphatic clearance dysfunction is correlated with the severity of CSVD [53]. It is plausible to speculate that the hydrodynamic force driven glymphatic clearance is inherently affected by a dysfunction of SMCs.

3.5. Disorder of CBF Regulation

CBF refers to the volume of blood passing through a given volume of brain tissue over a specified period. CBF autoregulation is realized through vasodilation or vasoconstriction in response to blood demand and mechanical stress from blood pressure. Besides perfusion pressure acting on blood vessels, CBF is primarily determined by three physiological processes (Figure 3). Firstly, CBF is intricately regulated at a local level, responding to metabolite within brain tissue. For instance, carbon dioxide (CO₂) acts as a vasodilator by altering pH levels, influencing ion channel conductance in vascular SMCs [54]. However, impaired CO₂ response increases CSVD burden and worsened cognitive function [55,56]. Secondly, the myogenic response refers to blood vessel constriction in response to elevated intravascular pressure, while dilation upon pressure reduction [57]. The impairment of this response can be found in CSVD such as CADASIL [58]. Notch3-KO mice, modeling CADASIL with arterial smooth muscle cell loss, exhibit significantly reduced myogenic tone in pial arteries, severely compromising CBF autoregulation [59]. In another hereditary CSVD associated with COL4A1 gene mutations, an age-related decline in myogenic tone is observed in cerebral arteries [35]. Thirdly, neurovascular coupling (NVC), also known as functional hyperemia, performs additional role in regulating CBF. NVC involves neural activity-dependent increases in CBF to meet localized metabolic demands for nutrients and oxygen. This intricate process involves neural signal transmission through three distinct pathways: astrocytic endfeet, interneuron synapses, or endothelial projections targeting smooth muscle cells (SMCs). These pathways collectively trigger vasodilation in response to neuronal activity [60,61]. A systematic review investigating NVC's relationship with CSVD revealed that 26 out of 29 studies reported diminished NVC with increasing severity of CSVD [62]. Dynamic CBF autoregulation was found to be impaired in patients, with the extent of this impairment being positively correlated with the burden of CSVD markers on MRI [63]. Overall, these studies underscore the key role of compromised NVC and myogenic response in the underlying mechanisms of CSVD, thereby emphasizing their potential as promising therapeutic targets for addressing this condition.

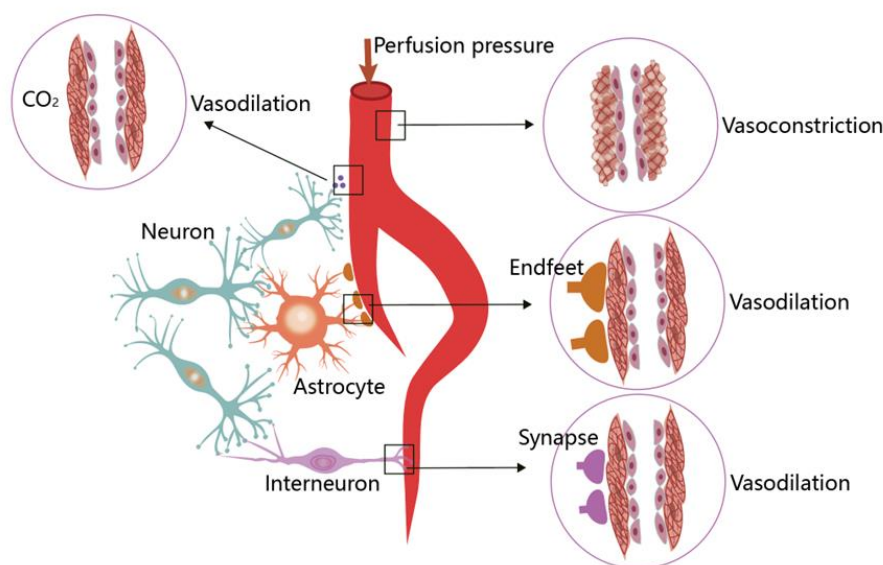


Figure 3. Physiological processes of CBF regulation. CBF regulation is a complex interplay of three key physiological processes: metabolic autoregulation, myogenic response, and NVC. Local metabolic regulation ensures CBF adapts to tissue demands, exemplified by CO₂-mediated vasodilation via pH changes in SMCs. The myogenic response maintains vascular tone through pressure-dependent constriction and dilation. NVC dynamically aligns CBF with neuronal activity through astrocytic, interneuronal, and endothelial signaling pathways.

4. Signaling Molecules Modulating SMCs

The hemodynamic conditions within the vasculature exert SMCs with constant mechanical stress, including forces such as transmural pressure, pulsatile pressure, and shear stress. Previous studies have shown that the functional and structural changes in SMCs are regulated by a variety of chemical and mechanical signals. Among chemical signals, the Notch3 receptor, predominantly expressed in SMCs, is essential for all phases of intracranial vascular development. One study suggested that age-related arterial loss of SMCs may be linked to a decrease in Notch3 signaling activity [64]. Additionally, endothelium-derived nitric oxide (NO) relaxes SMCs and subsequently promotes blood vessel dilation [65]. NO induces vasodilation by increasing cyclic guanosine monophosphate (cGMP) in SMCs [66]. Similar to cGMP, cyclic adenosine monophosphate (cAMP) also involved in regulating the relaxation of cerebrovascular SMCs [14]. The degradation of cGMP and cAMP is regulated by phosphodiesterases (PDEs). Notably, PDEs serve as crucial targets for modulating the degradation of cGMP and cAMP [9]. Moreover, endothelin-1 (ET-1) activate receptors on SMCs, causing vasoconstriction. Elevated ET-1 releasing by dysfunctional endothelial cells contributes to pathological vasoconstriction. Injections of ET-1 plus a nitric oxide synthase inhibitor into the cerebral issue induce vasoconstriction of small vessels, mimicking small vascular pathologies and resulting in clinical features [67]. Additionally, TGF- β is implicated as a key factor in the arterial SMCs depletion, and experiment with COL4A1-altered mice observe an increased TGF- β activity [34]. Last but not least, platelet-derived growth factor receptor-beta (PDGFR- β) signaling expressed by pericyte-like cells, is associated with the loss of SMCs in CADASIL [68].

The signaling pathways induced by mechanical stress in SMCs require further investigation in the context of CSVD. The activation of these proteins triggers multiple downstream signaling pathways simultaneously, leading to the expression and repression of various genes. The resulting cellular effects include proliferation, migration, phenotype changes, vasoconstriction, and alterations in ECM composition [17]. Several transmembrane proteins are under consideration as candidates, notably mechanosensitive ion channels [69], G protein-coupled receptors [70], cyclic nucleotide-gated

(CNG) ion channels [71], and focal adhesion kinase [72]. Collectively, despite the progress made, the complete understanding of the signals modulating SMCs is still under investigation.

5. Therapeutic Agents Targeting SMCs

The molecules implicated in the aforementioned pivotal signaling components can be regarded as potential pharmacological targets for regulating SMCs, presenting a promising avenue for the treatment of CSVD. Recent research endeavors have yielded encouraging exemplars, fostering optimism in this field. In the context of regulating cGMP, cytosolic cGMP undergoes degradation facilitated by phosphodiesterase 5 (PDE5). PDE5 exists within the SMCs that line the blood vessels of the human subcortical white matter. Tadalafil, a PDE5 inhibitor, can cross the blood-brain barrier. In 2022, Pauls et al. published the first clinical randomized controlled trial of PDE5 inhibitors for the treatment of vascular cognitive impairment, finding that tadalafil administration increased CBF in subcortical areas, especially in within white matter hyperintensities [73]. In addition to PDE5 inhibitor, cilostazol is a selective PDE3 inhibitor. In patients with CSVD, cilostazol is more effective than aspirin in reducing the ultrastructural damage to the apparently normal brain white matter and in lowering the risk of ischemic vascular events [74]. Recently, the LACI-2 study designed to treat symptomatic CSVD reveals that cilostazol shows efficacy in reducing patient dependence and improving their spirit. When cilostazol used in combination with isosorbide mononitrate, additional benefits can be observed [75].

6. Discussion

SMCs perform a central role in vascular homeostasis, orchestrating blood flow control, structural remodeling, and waste clearance. The dysfunction and quantitative changes in SMCs are increasingly recognized as key mechanisms in the development of CSVD. Vascular high-risk factors like chronic hypertension, genetic mutations, and aging disrupt these functions, leading to SMCs hypertrophy, loss, and phenotypic instability. Above pathological changes impair cerebral blood flow autoregulation, promote extracellular matrix disorganization, and reduce capacity of glymphatic clearance. These effects act synergistically to contribute to ischemic damage and cognitive decline.

The molecular mechanisms of SMCs dysfunction imply potential therapeutic targets. For example, cyclic nucleotide signaling pathways, which govern SMC relaxation and blood vessel dilation, can be targeted using drugs like cilostazol and tadalafil. These phosphodiesterase inhibitors boost cyclic nucleotide levels, improving blood flow and reducing vascular resistance. Despite progress, critical challenges remain. Current therapies mainly alleviate symptoms rather than dealing with causes lead to SMCs dysfunction. The heterogeneity of CSVD complicates treatment development, because different subtypes may demand distinct interventions. For instance, sporadic and hereditary forms may need different treatment methods. Although phosphodiesterase inhibitors improve blood flow, their effects on stabilizing SMCs phenotypes or restoring glymphatic clearance are unclear. In addition, crosstalk mechanisms such as endothelial damage, inflammation, and vascular aging likely interact with SMCs pathology, emphasizing the need for integrated therapeutic strategies.

To gain a profound understanding of the pathogenesis of CSVD, future research should focus on how mechanical forces and biochemical signals work together to cause SMCs dysfunction in specific CSVD subtypes. Currently, established techniques such as DTI-ALPS and dynamic cerebral blood flow imaging can non-invasively monitor SMC-mediated pathological changes in patients. Meanwhile, some mechanisms like endothelial-mesenchymal transition deserves attention. This process has been widely discussed in cardiovascular diseases and may provide new perspectives on the adaptive changes of SMCs. If the above-mentioned techniques are combined with molecular mechanism research, it can not only reveal the complex interactions between SMCs, inflammatory pathways, and endothelial repair, but also promote the shift of treatment strategies from symptomatic treatment to disease modification, ultimately improving outcomes for CSVD patients.

7. Conclusions

SMCs dysfunction is a crucial factor in the development of CSVD pathogenesis, leading to cerebral blood flow disorder, vascular structure damage, and metabolic waste accumulation. Although therapies targeting cyclic nucleotide signaling show early promise, a deeper understanding of the molecular mechanism of SMCs phenotypic switching and extracellular matrix dysregulation is essential. Future research should integrate multidisciplinary approaches, ranging from the exploration of molecular mechanisms to the application of advanced imaging techniques, from specific interventions on SMCs to the coordinated regulation of inflammation and endothelial repair. Such an integrated strategy may pave the way for effective treatments to relieve the rising global burden of CSVD.

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Abbreviations

CADASIL	Cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy
CARASIL	Cerebral autosomal recessive arteriopathy with sub-cortical infarcts and leukoencephalopathy
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CBF	Cerebral blood flow
CSF	Cerebrospinal fluid
CSVD	Cerebral small vessel disease
ECM	Extracellular matrix
NO	Nitric oxide
NVC	Neurovascular coupling
SMCs	Smooth muscle cells

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