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Review

Mitochondrial dysfunction in cerebrovascular diseases

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Mitochondria are central regulators of cerebrovascular health through their control of energy metabolism, Ca^{2+} homeostasis, and redox signaling, and their dysfunction represents a convergent pathogenic mechanism across cerebrovascular diseases. In ischemic stroke, mitochondrial failure exacerbates neuronal injury via permeability transition pore opening, oxidative stress, and bioenergetic collapse, while altered mitochondrial dynamics and the release of mitochondrial damage-associated molecular patterns amplify neuroinflammation during reperfusion. Beyond stroke, mitochondrial dysfunction contributes to intracranial aneurysms, atherosclerotic stenosis, and vascular malformations, where oxidative stress, mitochondrial DNA instability, and cell type-specific metabolic reprogramming drive vascular remodeling and lesion progression. In this review, we integrate recent evidence highlighting context- and stage-dependent roles of mitochondria in cerebrovascular pathology and discuss implications for biomarker discovery, therapeutic targeting, and translational strategies.

Highlights

Opening of the mitochondrial permeability transition pore, Ca^{2+} overload, and mitochondrial fragmentation are early features of stroke-induced brain injury observed in experimental models.

Mitochondrial reactive oxygen species and activation of the cyclophilin D–reactive oxygen species–NLR family pyrin domain-containing 3–matrix metalloproteinase-9 axis are associated with intracranial aneurysm progression, linking mitochondrial stress to vascular wall instability.

Disruption of mitochondrial homeostasis exacerbates vascular pathology in intracranial atherosclerotic stenosis, arteriovenous malformations, and cavernous malformation, indicating a shared mitochondrial contribution across cerebrovascular disorders.

Pharmacological modulation of mitochondrial permeability, redox signaling, proprotein convertase subtilisin/kexin type 9, and mechanistic target of rapamycin kinase pathways shows robust preclinical efficacy, while clinical outcomes remain heterogeneous.

Experimental studies support the feasibility of mitochondrial transplantation in models of cerebrovascular injury, including stroke.

Mitochondria as central regulators of cerebrovascular pathology

Cerebrovascular diseases comprise a heterogeneous group of conditions affecting cerebral blood vessels and brain circulation, resulting in impaired oxygen and nutrient delivery due to vessel deformation or damage [1]. These disorders are among the leading contributors to reduced human lifespan and quality of life [2]. They encompass a broad spectrum of pathological entities, including stroke, aneurysms, vascular stenosis, and vascular malformations [3].

Stroke is one of the primary causes of mortality and long-term disability in Western societies [4], arising from either occlusion or rupture of cerebral vessels. The severity of a stroke depends on the size and location of the affected brain area [5]. Aneurysms involve the dilation and potential rupture of weakened vessels, frequently resulting in life-threatening **subarachnoid hemorrhage (SAH)** (see Glossary). On the other hand, vascular stenosis refers to the pathological narrowing of cerebral arteries, while vascular malformations denote abnormal connections and structures within the vascular network [6]. Despite their clinical heterogeneity, these conditions share a set of converging molecular and cellular mechanisms, including redox imbalance, endothelial dysfunction, exacerbated inflammation, extracellular matrix remodeling, hemodynamic stress, and cell death induction [7]. Many of these processes converge, directly or indirectly, on mitochondrial function, consistent with the central role of mitochondria in ATP production, metabolic regulation, Ca^{2+} homeostasis, reactive oxygen species (ROS) generation, and the control of regulated cell death pathways [8–10]. Although mitochondrial dysfunction is a common feature of cerebrovascular diseases, its cellular origins and pathogenic significance differ markedly. In some conditions, such as aneurysms, stenosis, and vascular malformations, mitochondrial alterations may act as primary drivers of vascular wall degeneration, whereas in

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ischemic stroke and aneurysmal SAH, they often function as secondary amplifiers of neuronal injury [11,12]. These divergent roles nonetheless give rise to a partially shared spectrum of mitochondrial functional and structural abnormalities. In this context, mitochondrial dynamics, governed by the balance between fusion and fission events, are critical for maintaining mitochondrial integrity and cellular homeostasis (Box 1), especially in energy-demanding tissues like the brain [13]. An imbalance toward mitochondrial fragmentation increases cellular vulnerability to stress and predisposes to cell death, whether driven by impaired fusion or excessive fission activity [17,18]. Similar detrimental effects arise from mitochondrial functional alterations, including redox imbalance caused by impaired antioxidant defense or defective oxidative phosphorylation (OXPHOS) [19], as well as disrupted mitochondrial Ca^{2+} homeostasis, which may result from deregulation of the mitochondrial calcium uniporter (MCU) complex (MCUc), the main route for Ca^{2+} entry into the mitochondrial matrix [20]. Importantly, the selective removal of damaged mitochondria through mitophagy [15] has emerged as a protective mechanism in multiple pathological contexts, including cerebrovascular diseases (Box 1).

From a metabolic perspective, mitochondrial dysfunction in cerebrovascular diseases plays a pivotal role in shaping neuronal fate as well as the immunophenotype of microglia and infiltrating myeloid cells. In particular, mitochondrial metabolic reprogramming, characterized by alterations in the complex I/IV ratio, changes in complex I activity [21], increased glycolysis, and the consequent accumulation of succinate, has emerged as a key mechanism driving the polarization of microglia and infiltrating myeloid cells toward a proinflammatory phenotype [22].

In this review, we synthesize current evidence on how mitochondrial dysfunction contributes to the pathogenesis of major cerebrovascular diseases. By integrating molecular mechanisms with clinical and translational perspectives, we aim to critically evaluate both therapeutic opportunities and the key limitations that currently hinder effective clinical translation.

Mitochondrial dysfunction in stroke

Stroke is broadly classified into two major types: ischemic and hemorrhagic, which account for approximately 80% and 20% of all cases, respectively [23].

Box 1. Mitochondrial dynamics and quality control in cerebrovascular disease

Mitochondrial homeostasis is maintained through a highly dynamic network of processes that regulate mitochondrial morphology, turnover, and functional integrity. Among these mechanisms, mitochondrial fission and fusion play essential roles in preserving mitochondrial bioenergetics and cellular viability under physiological and pathological conditions. Mitochondrial fission is primarily mediated by the GTPase DRP1, which is recruited from the cytosol to the outer mitochondrial membrane to constrict and divide mitochondria. By contrast, mitochondrial fusion is mainly regulated by the outer membrane proteins MFN1/2 and the inner membrane GTPase OPA1, which coordinate the merging of mitochondrial membranes and the maintenance of cristae architecture [13].

In cerebrovascular diseases, dysregulation of mitochondrial dynamics has been reported in multiple cellular components of the neurovascular unit [14]. For example, excessive DRP1-mediated mitochondrial fragmentation in neurons, contributing to bioenergetic failure and promoting apoptotic signaling following ischemic injury. In endothelial cells, altered mitochondrial dynamics may compromise vascular integrity and contribute to BBB dysfunction. Similarly, mitochondrial remodeling in VSMCs may influence vascular tone and structural stability, whereas in microglia and infiltrating myeloid cells, mitochondrial metabolic reprogramming is closely associated with inflammatory activation.

Mitochondrial quality control is further maintained through mitophagy, a selective autophagic process that eliminates damaged mitochondria and prevents the accumulation of dysfunctional organelles. Impaired mitophagy has been increasingly recognized as a contributing factor in cerebrovascular pathology, where the persistence of dysfunctional mitochondria can exacerbate oxidative stress, inflammatory signaling, and neuronal injury [15]. However, dysregulated mitophagy may also be detrimental in certain contexts, as deletion of the mitophagy receptor BCL2-interacting protein 3 (BNIP3) has been shown to be neuroprotective in ischemic stroke models by mitigating the excessive mitophagy associated with neuronal cell death [16].

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Stroke results from focal brain injury driven by irreversible cellular damage, triggered by either obstruction or rupture of cerebral blood vessels. The ensuing reduction in cerebral blood flow or intracerebral hemorrhage disrupts cellular homeostasis and initiates a cascade of deleterious biochemical events closely linked to mitochondrial dysfunction, including oxidative stress, ATP depletion, and inflammation, ultimately culminating in cell death [24]. Within the **ischemic penumbra**, apoptotic cell death predominates [25], whereas the **ischemic core** is characterized by multiple nonapoptotic forms of cell death, including mitochondrial permeability transition (MPT)-driven necrosis, ferroptosis, and necroptosis [26] (Box 2).

Although necroptotic cell death has been described in multiple animal models of ischemic stroke [34], mitochondrial alterations are generally not considered the primary initiating event but rather act as amplifiers of necroptotic injury once the receptor-interacting protein kinase 1/3 (RIPK1/RIPK3)–mixed lineage kinase domain-like protein (MLKL) pathway has been engaged. Accordingly, in an *in vitro* model of ischemia–reperfusion (I/R) injury, MLKL localizes to mitochondria and interacts with the pore-forming protein voltage-dependent anion channel 1 (VDAC1), inducing its oligomerization and subsequent outer mitochondrial membrane permeabilization, thereby exacerbating, but not initiating, cell death [11]. Conversely, excessive ROS production or massive mitochondrial Ca^{2+} accumulation act as *bona fide* activators of the mitochondrial permeability transition pore complex (PTPC), resulting in MPT and regulated necrosis. Seminal studies demonstrated that mice lacking cyclophilin D (CYPD, encoded by the *Ppif* gene) exhibit reduced infarct volumes and improved neurological outcomes following I/R injury [35]. On this basis, PTPC inhibition emerged as one of the earliest neuroprotective strategies to limit neuronal loss after ischemic stroke. Consistently, pharmacological inhibition of the PTPC with agents such as

Box 2. Necrosis, necroptosis, and ferroptosis: divergent mechanisms of regulated cell death

MPT-driven necrosis arises from mitochondrial dysfunction that triggers sustained opening of the mitochondrial PTPC. Excessive Ca^{2+} uptake, oxidative stress, and adenine nucleotide depletion promote high-conductance PTPC opening, a pathological state that collapses membrane potential, blocks ATP synthesis, induces matrix swelling, and ruptures the outer mitochondrial membrane, a sequence of events particularly relevant during I/R injury [27]. By contrast, low-conductance or transient PTPC opening allows controlled solute flux and can release cytochrome c to activate apoptosis in energy-competent cells. Thus, the amplitude and duration of PTPC opening dictate whether cells undergo apoptosis or necrosis. The pore's regulation depends on CYPD, while structural evidence implicates the F_1F_0-ATP synthase, particularly its c-subunit ring and OSCP, as key pore-forming and CYPD-interacting elements. Additional regulatory components proposed to participate in PTPC modulation include the adenine nucleotide translocator in the inner mitochondrial membrane and the VDAC in the outer mitochondrial membrane, which together may facilitate metabolite exchange and mitochondrial permeability changes during stress conditions. MPT-driven necrosis culminates in plasma-membrane rupture and release of mitoDAMPs such as mtDNA and ATP, amplifying inflammation [28].

Necroptosis is a genetically programmed form of necrosis initiated when caspase-8 is inhibited. Under these conditions, RIPK1 and RIPK3 assemble the necrosome, leading to phosphorylation of MLKL. Phosphorylated MLKL oligomerizes and inserts into the plasma membrane to form disruptive pores, causing ionic imbalance and lytic death [29]. Mitochondria participate indirectly: RIPK3 stimulates mitochondrial ROS, and activated MLKL can damage mitochondrial membranes, reinforcing cell demise. Necroptosis is highly inflammatory, releasing DAMPs that engage Toll-like receptors, NLR family pyrin domain containing 3 (NLRP3), and the cGAS–STING pathway [30].

Ferroptosis is an iron-dependent form of regulated necrosis defined by the accumulation of phospholipid hydroperoxides [31,32]. Failure of glutathione peroxidase 4 (GPX4), particularly under glutathione depletion or impaired cystine import, allows uncontrolled lipid peroxidation. Labile iron drives Fenton chemistry, amplifying oxidative damage until membrane integrity fails. Ferroptotic mitochondria are characteristically shrunken with dense membranes and reduced cristae, differing from the swollen mitochondria of MPT-driven necrosis and necroptosis. Although mitochondria are not strictly required, their metabolic state, including tricarboxylic acid cycle (TCA) cycle flux, electron transport chain activity, and mitochondrial ROS, modulates ferroptotic sensitivity [33].

Together, these pathways exemplify distinct biochemical routes to regulated cell lysis, each with specific molecular triggers and inflammatory consequences.

Glossary

Circle of Willis: an arterial anastomotic network located at the base of the brain that connects the anterior and posterior cerebral circulations. It provides collateral blood flow to preserve cerebral perfusion in the event of proximal arterial stenosis or occlusion.
Cyclosporine A (CsA): a cyclic undecapeptide with potent immunosuppressive properties. In the context of mitochondrial biology, CsA modulates mitochondrial calcium handling and inhibits the opening of the PTPC through cyclophilin D inhibition. Nonimmunosuppressive CsA analogs, such as NIM811, retain mitochondrial activity while minimizing systemic immunosuppression.
Early brain injury: a term describing the cascade of secondary brain damage occurring within the first 72 h after subarachnoid hemorrhage. Clinically, early brain injury includes abrupt intracranial pressure elevation, reduced cerebral blood flow, impaired autoregulation, blood–brain barrier disruption, cerebral edema, neuroinflammation, oxidative stress, and neuronal cell death.
Hereditary hemorrhagic telangiectasia (HHT): a rare autosomal dominant vascular disorder characterized by abnormal blood vessel formation. Mutations commonly affect the ENG, ACVRL1, or SMAD4 genes and result in recurrent bleeding, anemia, and arteriovenous malformations.
Ischemic core: the region of brain tissue subjected to severe and sustained cerebral blood flow interruption, resulting in rapid and irreversible cellular injury.
Ischemic penumbra: the hypoperfused brain region surrounding the ischemic core, characterized by functionally impaired but potentially salvageable tissue if timely reperfusion is achieved.
Neurovascular unit: a dynamic, multicellular structure composed of endothelial cells, neurons, astrocytes, pericytes, and vascular smooth muscle cells. Coordinated interactions among these components regulate cerebral blood flow, energy metabolism, and blood–brain barrier integrity.
Subarachnoid hemorrhage (SAH): acute bleeding into the subarachnoid space, most often caused by the rupture of an intracranial aneurysm. A major delayed complication is delayed cerebral ischemia, a leading contributor to poor

cyclosporine A (CsA) or NIM811 produced neuroprotective effects in preclinical stroke models [36,37]. However, chronic cyclosporine treatment in humans is associated with increased blood pressure, thereby augmenting stroke risk [38], and intravenous cyclosporine administered in combination with thrombolysis failed to reduce infarct size in patients with acute anterior-circulation stroke [39] (see also 'Mitochondria-targeted therapeutic strategies and clinical trials in cerebrovascular disease' section).

The emerging involvement of F_1F_0-ATP synthase components in PTPC formation (Box 2) has opened alternative mechanistic perspectives. Purified c-subunits of ATP synthase form high-conductance, Ca^{2+}- and CsA-sensitive channels, while conformational rearrangements, such as dissociation of the F_1 sector, promote pore opening during excitotoxic ischemic injury [40,41]. Furthermore, the oligomycin sensitivity-conferring protein (OSCP) subunit modulates PTPC responsiveness to pH and Ca^{2+}, and its destabilization renders mitochondria more prone to pore opening [42]. Pharmacological stabilization of F_o–OSCP interactions or inhibition of c-ring components limits PTPC opening and reduces infarct size in preclinical I/R models [43,44]. However, whether ATP synthase-mediated PTPC inhibition can translate into a robust and clinically meaningful therapeutic effect remains unresolved.

By controlling mitochondrial Ca^{2+} uptake, the MCUc exerts a major influence on PTPC opening. In ischemic postconditioning models, pharmacological inhibition of MCU using ruthenium red analogs, such as Ru265, attenuates mitochondrial depolarization and limits PTPC opening, thereby supporting neuronal survival after reperfusion [45]. Both pharmacological and genetic inhibition of MCUc preserve **neurovascular unit** integrity by preventing mitochondrial Ca^{2+} overload, which otherwise drives PTPC-mediated cell death and secondary blood–brain barrier (BBB) disruption [46]. In line with this, *in vivo* deletion of *mcub*, which encodes an inhibitory MCUc subunit, enhances mitochondrial Ca^{2+} accumulation and exacerbates brain damage in a transient middle cerebral artery occlusion model [47]. Finally, proline-rich tyrosine kinase 2, which promotes mitochondrial Ca^{2+} uptake by phosphorylating MCU, is activated during cerebral ischemia, contributing to mitochondrial dysfunction and cell death [48] (Figure 1). Despite strong experimental support for MCUc as a regulator of mitochondrial Ca^{2+} homeostasis and PTPC activation, no MCUc-targeting compounds have yet advanced to clinical testing in stroke.

Besides necrosis, accumulating evidence identifies ferroptosis as a major contributor to neuronal injury after ischemic stroke [49]. Mitochondrial dysfunction is tightly intertwined with ferroptosis, acting both upstream and downstream of ferroptotic signaling. During I/R, excessive mitochondrial ROS generation, impaired electron transport, and iron accumulation promote lipid peroxidation [50]. Morphologically, ferroptotic cells display mitochondrial shrinkage, cristae loss, and increased membrane density—features distinct from apoptosis or necrosis (Figure 1). Importantly, inhibition of oxidative metabolism or mitochondrial ROS production suppresses ferroptotic signaling during the early phase of injury, for instance, through targeting glutaminolysis or the electron transport chain [33]. By contrast, long-term enhancement of mitochondrial function, such as by overexpressing mitochondrial ferritin or activating peroxisome proliferator-activated receptor-γ coactivator 1α, markedly attenuates ferroptosis in cerebral I/R models [51,52], likely by improving mitochondrial antioxidant capacity and iron handling. Thus, the role of mitochondria in ferroptosis appears to be context dependent, with acute suppression of mitochondrial ROS limiting ferroptotic initiation, whereas improved mitochondrial homeostasis can increase resistance to ferroptotic damage. Notably, recent observations implicate close endoplasmic reticulum–mitochondria contacts in ferroptosis induction [53], although their contribution to stroke pathogenesis remains unexplored. Collectively, these findings support mitochondrial dysfunction as a driver, rather than a mere consequence, of ferroptotic injury in stroke.

neurological outcomes in patients with SAH.

VSMC phenotypic switching: the transition of vascular smooth muscle cells from a differentiated, contractile phenotype to a synthetic, less differentiated state. This process is characterized by reduced expression of contractile proteins (e.g., α-smooth muscle actin) and increased matrix metalloproteinase activity, which contributes to extracellular matrix remodeling and vascular instability.

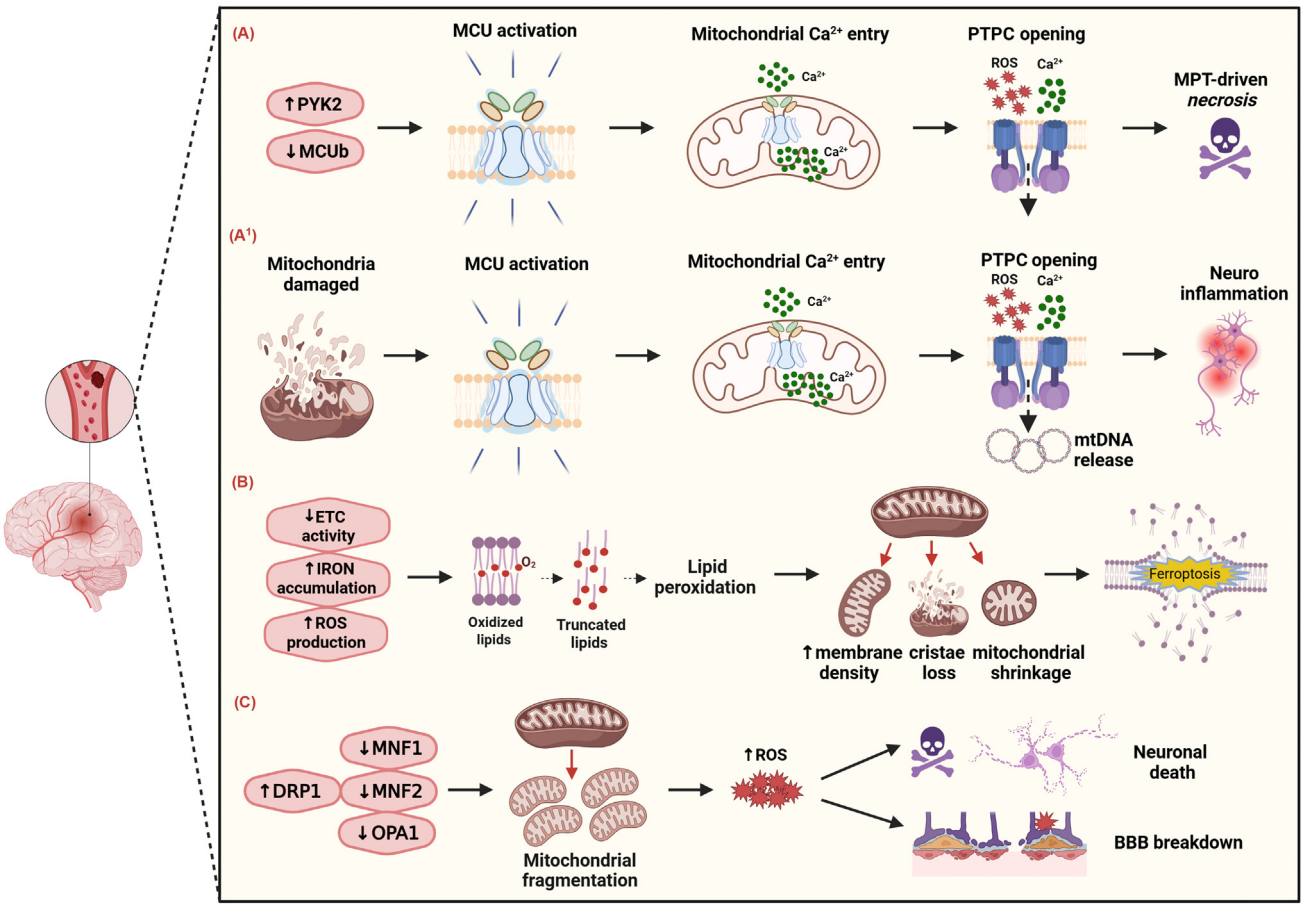

Figure 1. Mitochondria-related mechanisms regulating stroke. (A) Activation of the MCUc, via PYK2-mediated phosphorylation or MCUb downregulation, triggers excessive mitochondrial Ca^{2+} uptake, leading to PTPC opening and culminating in MPT-driven necrosis. In parallel, mitochondrial stress associated with MCUc activation promotes Ca^{2+}-dependent PTPC opening and release of oxidized mtDNA, thereby contributing to neuroinflammation (A^1). (B) Enhanced ROS generation, ETC dysfunction, and iron accumulation drive lipid peroxidation and ferroptosis, characterized by distinct mitochondrial alterations, including shrinkage, cristae loss, and increased membrane density. (C) Finally, pronounced mitochondrial fragmentation caused by DRP1 upregulation or MFN1/2 or OPA1 downregulation is linked to excessive ROS production, neuronal death, or BBB disruption in cerebrovascular cells. BBB: blood–brain barrier; DRP1: dynamin-related protein 1; ETC: electron transport chain; MCUb: mitochondrial calcium uniporter b; MCUc: mitochondrial calcium uniporter complex; MFN1/2: mitofusin 1/2; MPT: mitochondrial permeability transition; mtDNA: mitochondrial DNA; OPA1: optic atrophy 1; PTPC: permeability transition pore complex; PYK2: proline-rich tyrosine kinase 2; ROS: reactive oxygen species. Created in https://biorender.com.

Beyond the direct induction of cell death pathways, mitochondrial dysfunction in stroke is also characterized by profound alterations in mitochondrial dynamics, including imbalances between fission and fusion that further compromise neuronal viability (Figure 1). During ischemic stroke, mitochondrial dynamics shift toward excessive fission across multiple cellular components of the neurovascular unit, including neurons and cerebrovascular endothelial cells, characterized by increased dynamin-related protein 1 (DRP1) activity, reduced mitofusin 1/2 (MFN1/2)-mediated fusion, and impaired optic atrophy 1 (OPA1)-dependent inner membrane integrity (Box 1). Focal I/R rapidly induces DRP1 upregulation and mitochondrial fragmentation in neurons, promoting ROS accumulation, cytochrome c release, and cell death [54]. Pharmacological DRP1 inhibition with Mdivi-1 restores mitochondrial membrane potential and reduces infarct size in rodent models [55]. Nonetheless, DRP1 activation also occurs in cerebrovascular endothelial cells during ischemia, promoting mitochondrial

dysfunction and BBB breakdown, thereby contributing to increased neuronal vulnerability within the neurovascular unit [56]. Similarly, the levels of the pro-fusion MFN2 protein are significantly downregulated following I/R, impairing mitochondrial networking and Ca^{2+} homeostasis; re-expression of MFN2 supports mitochondrial integrity and increases neuronal viability *in vitro* [57].

In addition to regulating cell survival, mitochondria act as central mediators of poststroke neuroinflammation through the release of damage-associated molecular patterns (DAMPs). Stroke-associated BBB disruption permits the diffusion of inflammatory cytokines and chemokines released by injured neurons, including IL-6 and IL-1β, into surrounding brain tissue [58]. Mitochondrial dysfunction critically contributes to this process, as damaged mitochondria release mitochondrial DAMPs (mitoDAMPs), such as mitochondrial DNA (mtDNA), which activate innate immune signaling cascades [9]. Intriguingly, upon mitochondrial damage, Ca^{2+} entry via the MCUc triggers the PTPC opening, thereby promoting mtDNA spillage and consequent inflammation [59].

In addition to mtDNA, mitochondrial damage leads to the release of other mitoDAMPs, including cardiolipin, *N*-formyl peptides, and mitochondrial ROS (mtROS). These signals activate innate immune pathways through at least two major inflammatory cascades. The first involves the DNA-induced cyclic GMP–AMP synthase (cGAS)–cyclic GMP–AMP (cGAMP)–stimulator of interferon genes (STING) signaling axis, which promotes interferon production and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-dependent cytokine expression in stressed glial cells [60]. The second pathway is triggered by mitoDAMPs such as mtDNA and mtROS, which promote the cytoplasmic assembly of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. This multiprotein complex converts pro-caspase-1 into active caspase-1, ultimately leading to the release of IL-1β and IL-18 in activated glial cells [9]. In addition, mtDNA can directly bind Toll-like receptor 9 in neighboring cells, promoting NF-κB nuclear translocation and amplifying the production of proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and IL-6, thereby propagating neuroinflammation within the injured brain tissue [60].

Mitochondrial dysfunction in intracranial aneurysm

While traditional genetic and hemodynamic factors have long been implicated in intracranial aneurysm (IA) formation, a growing body of evidence has highlighted mitochondrial dysfunction as a central contributor to its pathogenesis [61,62]. IA is a pathological dilation of a cerebral artery, most frequently arising at the **circle of Willis**, resulting from the weakening of the vessel wall [63], which can evolve toward rupture, causing SAH and severe neurological outcomes. Importantly, although neuronal and glial cells do not participate in aneurysm wall degeneration and do not display overt mitochondrial defects during aneurysm formation, rupture-induced SAH rapidly triggers severe mitochondrial injury in neurons, including depolarization, swelling, mtDNA damage, and oxidative stress, thereby contributing to **early brain injury** [12].

Based on morphology, IAs are classified into saccular, fusiform, dissecting, mycotic, marantic, and blister types, with saccular aneurysms accounting for over 90% of cases [64]. A hallmark of IA pathology is extensive oxidative damage to proteins, lipids, and DNA within the aneurysmal wall, particularly in vascular smooth muscle cells (VSMCs), endothelial cells, and infiltrating macrophages. This damage is driven by impaired mitochondrial electron transport, hemoglobin auto-oxidation, and activation of pro-oxidant enzymes [65–67]. Sustained redox imbalance promotes progressive wall degeneration, thereby increasing susceptibility to rupture. In this context, genetic deletion of the p47phox subunit of NADPH oxidase or pharmacological treatment with the free radical scavenger edaravone significantly reduces aneurysm incidence

in rat IA models [68]. Complementary insights from high-throughput omics approaches have further refined the molecular landscape of mitochondrial dysfunction in IA, identifying four oxidative stress-related genes (*FLVCR2*, *SDSL*, *TBC1D2*, and *SLC31A1*) whose expression correlates with ROS pathway activation, metabolic dysregulation, and macrophage- and mast cell-mediated inflammation [69]. Accordingly, intracellular Ca^{2+} entry driven by transient receptor potential canonical 6 (TRPC6) upregulation induces transcription of NADPH oxidase 4 (NOX4), an important source of ROS mainly located at the inner mitochondrial membrane [70], promoting **VSMC phenotypic switching** [71] (Figure 2). Although direct evidence in IA is currently lacking, cardiovascular studies suggest that this phenotypic transition is not exclusively ROS-driven but is also tightly coupled to specific mitochondrial defects, including mtDNA instability, cristae disorganization, and altered fission–fusion dynamics, which reshape VSMC identity and favor a synthetic, pro-remodeling state [72].

In parallel with ROS overproduction, nitric oxide (NO) has emerged as an additional mitochondrial stressor in aneurysmal pathology, contributing to both aneurysm development and mitochondrial dysfunction in the brain. Analysis of human and rat cerebral aneurysms revealed increased inducible nitric oxide synthase (iNOS) expression selectively at aneurysm sites, but not in the healthy arterial wall [73]. This is mirrored by the accumulation of cerebral NO during the acute phase of SAH [74], thereby contributing to mitochondrial respiratory inhibition and the accumulation of metabolic byproducts, such as lactate and glutamate [75] (Figure 2).

As previously discussed in the context of stroke, activation of the PTPC may also play a critical role in IA pathogenesis. Elevated levels of CYPD have been detected in both human IA lesions and the aneurysmal walls of murine models [76]. Mechanistically, CYPD activation promotes

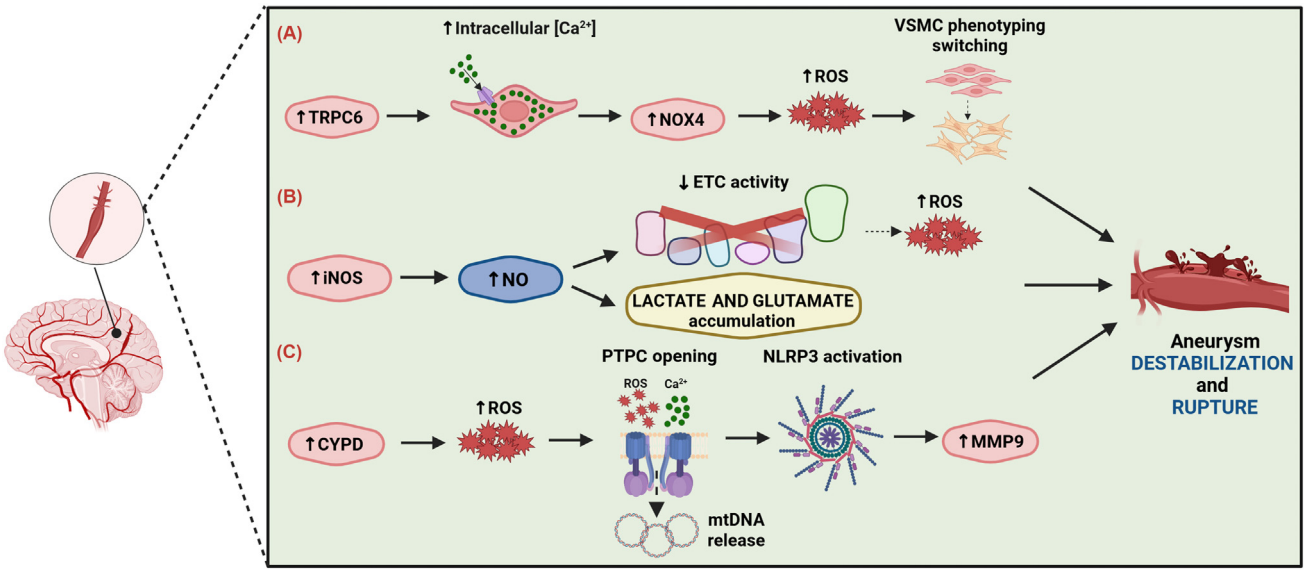

Figure 2. Mitochondrial control of IA development. (A) Elevated intracellular Ca^{2+} levels driven by TRPC6 promote NOX4 upregulation and enhanced mitochondrial ROS production, leading to VSMC phenotypic switching. (B) iNOS upregulation increases cerebral NO levels, resulting in ETC inhibition, ROS generation, and accumulation of lactate and glutamate. (C) Elevated CYPD levels enhance ROS production and promote PTPC opening, leading to oxidized mtDNA release, NLRP3 inflammasome activation, and MMP9 upregulation. Collectively, these mechanisms contribute to aneurysm destabilization and rupture. CYPD: cyclophilin D; ETC: electron transport chain; iNOS: inducible nitric oxide synthase; MMP9: matrix metalloproteinase-9; mtDNA: mitochondrial DNA; NLRP3: NLR family pyrin domain containing 3; NO: nitric oxide; NOX4: NADPH oxidase 4; PTPC: permeability transition pore complex; ROS: reactive oxygen species; TRPC6: transient receptor potential canonical 6; VSMC: vascular smooth muscle cells. Created in https://biorender.com.

PTPC opening and excessive ROS generation, which, in turn, triggers the activation of the NLRP3 inflammasome through mtDNA damage associated with 8-hydroxy-2′-deoxyguanosine (8-OHdG) formation, ultimately leading to the upregulation of MMP9 [76]. This CYPD/ROS/NLRP3–MMP9 signaling axis contributes to aneurysm destabilization and rupture (Figure 2), providing preclinical support for targeting mitochondrial pathways with CsA or related compounds. However, the mitochondrial defects driving CYPD upregulation and PTPC activation remain undefined. Likewise, it remains unclear whether the protective effects of CsA primarily reflect the inhibition of cell death or the suppression of mtDNA release. In the latter scenario, pharmacological inhibition of VDAC1, which cooperates with the PTPC to permit mtDNA efflux [77], or targeting NLRP3 might represent alternative therapeutic strategies.

Beyond MPT-driven necrosis (Box 2), mitochondrial dysfunction in IA contributes to multiple modes of regulated cell death, leading to the progressive loss of mural VSMCs. Cumulative depletion of these cells compromises aneurysm wall integrity and accelerates degenerative remodeling, thereby heightening rupture risk. Histological analyses of ruptured aneurysms demonstrate marked reductions in vascular wall cellularity, primarily mediated by caspase-9-dependent apoptosis, together with pronounced upregulation of the oxidative stress-responsive enzyme heme oxygenase-1, particularly in regions containing intraluminal thrombi and inflammatory infiltrates [66]. Intriguingly, single-cell analyses in murine aneurysm models indicate a metabolic shift in VSMCs, from increased OXPHOS and glycolysis during aneurysm formation to severe energy failure, mitochondrial collapse, and apoptotic signaling upon rupture, linking mitochondrial dysfunction to wall degeneration [78]. This suggests a disease stage-dependent role of mitochondrial metabolism, supporting VSMC proliferation during early phases while simultaneously generating deleterious byproducts, such as ROS, that promote mural cell depletion and structural destabilization. Additional transcriptomic datasets reveal enrichment of necroptosis-associated gene signatures in VSMCs and infiltrating macrophages [79]; however, several annotated genes (e.g., *BAX*, *NLRP3*, and *STAT1*) are only indirectly linked to canonical necroptotic pathways, suggesting activation of intersecting death programs. Consistently, ferroptosis-related gene signatures have also been identified in human IA samples [80], although whether these signatures reflect mitochondria-driven ferroptosis or broader oxidative stress responses remains unresolved.

Collectively, current evidence positions mitochondrial dysfunction as a central driver of IA pathogenesis, integrating oxidative stress, inflammation, vascular remodeling, and regulated cell death into a unified pathogenic framework.

Mitochondrial dysfunction in other cerebrovascular diseases

In contrast to stroke and aneurysms, where mitochondrial dysfunction has been extensively characterized, much less is known about its contribution to other cerebrovascular disorders such as intracranial and carotid stenosis, arteriovenous malformations (AVMs), and cerebral cavernous malformations (CCMs). In these conditions, the available evidence is sparse and often indirect, making their mitochondrial biology still largely unexplored.

Intracranial and carotid stenosis

Within the spectrum of intracranial and carotid stenotic diseases, intracranial atherosclerotic stenosis (ICAS), the most common cause of ischemic stroke worldwide, is considered the intracranial manifestation of atherosclerotic narrowing. Although it is often grouped with carotid stenosis because both share pathogenic features such as luminal narrowing, endothelial dysfunction, and chronic vascular inflammation, ICAS represents a biologically distinct entity, as intracranial arteries differ markedly from extracranial vessels in structure, hemodynamics, and inflammatory behavior [81].

Tissues with high aerobic demand, including the brain, are particularly vulnerable to mitochondrial dysfunction, and ICAS may therefore reflect not only systemic metabolic stress but also local susceptibility driven by pre-existing mitochondrial defects. Among these, mtDNA instability has emerged as a potential contributor to vascular pathology. Elevated mtDNA heteroplasmy has been reported in patients with carotid atherosclerotic plaques [82] (Figure 3). A specific deletion of a guanine at position 652 alters the structure of 12S rRNA, impairs mitochondrial protein synthesis, and has been associated with increased susceptibility to stenosis, whereas a guanine

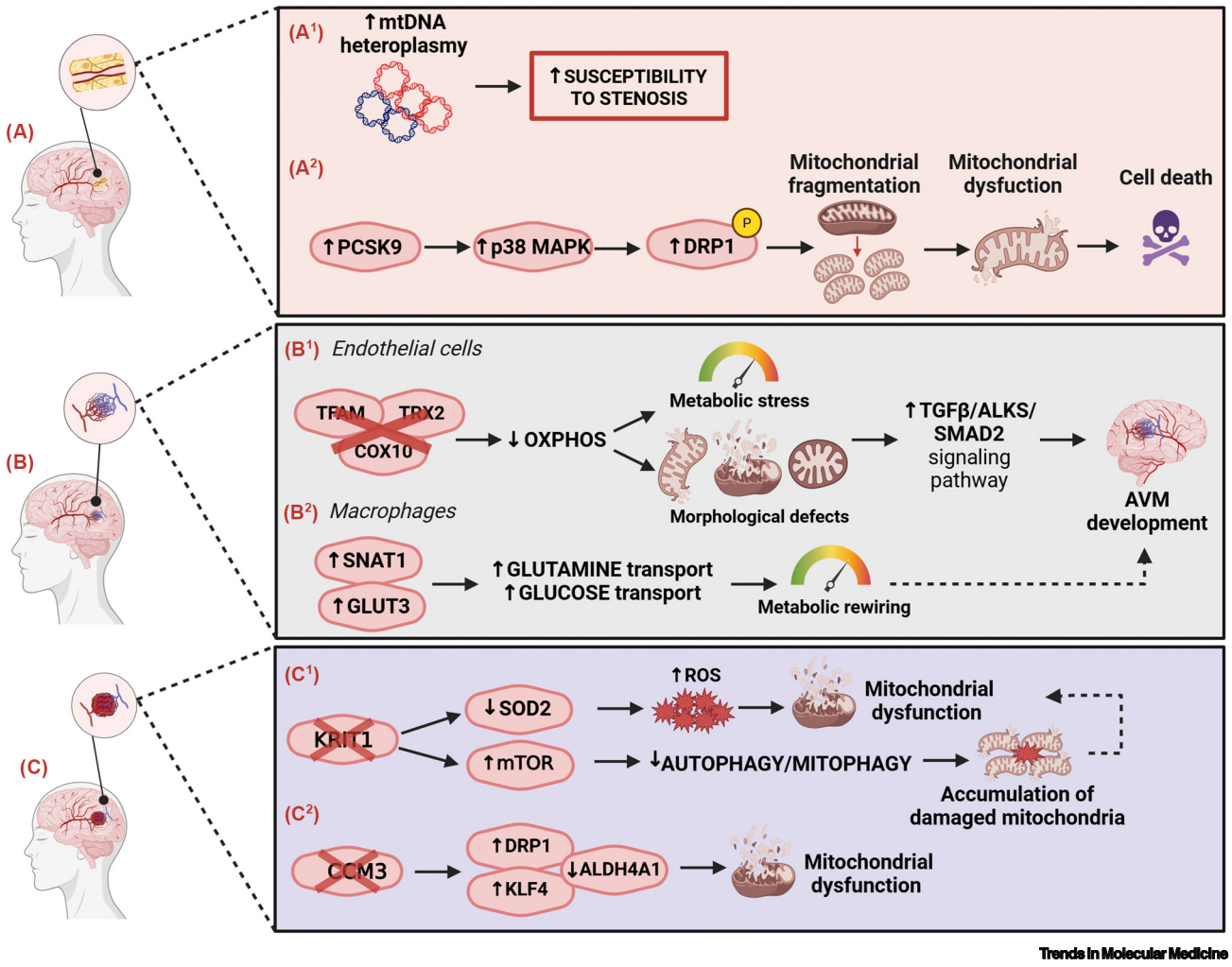

Figure 3. Mitochondrial alterations in other cerebrovascular diseases. (A) In ICAS, mtDNA heteroplasmy predisposes to stenosis (A^1), whereas PCSK9 upregulation activates p38 MAPK-dependent DRP1 phosphorylation, leading to mitochondrial fragmentation, dysfunction, and cell death (A^2). (B) In AVMs, loss of TFAM, TRX2, or COX10 in endothelial cells impairs OXPHOS, inducing metabolic stress and mitochondrial remodeling that activates the ALK5/SMAD2 signaling pathway and promotes AVM development (B^1). Concomitantly, SNAT1 and GLUT3 upregulation in macrophages supports metabolic rewiring that contributes to AVM formation (B^2). (C) In CCMs, KRIT1 loss drives mitochondrial dysfunction through oxidative stress resulting from SOD2 downregulation or impaired autophagy/mitophagy (C^1), with similar alterations observed upon CCM3 loss (C^2). ALDH4A1: aldehyde dehydrogenase 4 family member A1; ALK5: activin receptor-like kinase 5; AVMs: arteriovenous malformations; CCM3: cerebral cavernous malformations 3; CCMs: cerebral cavernous malformations; COX10: cytochrome c oxidase assembly factor heme A:farnesyltransferase; DRP1: dynamin-related protein 1; GLUT3: glucose transporter 3; ICAS: intracranial atherosclerotic stenosis; KLF4: Krüppel-like factor 4; KRIT1: Krev interaction trapped protein 1; MAPK: mitogen-activated protein kinase; MTOR: mechanistic target of rapamycin kinase; mtDNA: mitochondrial DNA; OXPHOS: oxidative phosphorylation; PCSK9: proprotein convertase subtilisin/kexin type 9; ROS: reactive oxygen species; SMAD2: SMAD family member 2; SNAT1: sodium-coupled neutral amino acid transporter 1; SOD2: superoxide dismutase 2; TGFβ: transforming growth factor beta; TFAM: transcription factor A, mitochondrial; TRX2: thioredoxin-2. Created in https://biorender.com.

Table 1. Mitochondria-based interventions for cerebrovascular diseases

Cerebrovascular disease	Drug	Model	Mitochondria-related and preclinical effects	Clinical trial	Refs
Stroke	Ru265	*In vitro*, animal models	Inhibited mitochondrial Ca^{2+} entry and PTPC opening. Convulsions in rodents.	Not done	[45]
Stroke	Mdivi-1	*In vitro*, animal models	Inhibition of DRP1-driven mitochondrial fission. Attenuation of infarct size and amelioration of neurological function. Low target specificity and limited brain bioavailability.	Not done	[55,107,108]
Stroke	CsA or analogs	*In vitro*, animal models, and humans	Decrease PTPC opening. Poor BBB permeability and neurotoxicity.	Phase 2, randomized Parallel assignment Double blind NCT01527240[a]	[36,37,39,109]
Stroke	MitoQ	*In vitro*, animal models, and humans	Decrease ROS burst and improve vascular function.	Phase 2, randomized Crossover assignment Double blind NCT06930638[b]	[112]
Stroke	Melatonin	*In vitro*, animal models, and humans	Decrease cardiolipin oxidation and PTPC opening.	Phase 3, randomized Parallel assignment Double blind NCT05857046[c]	[113]
Stroke	Deferoxamine mesylate	*In vitro*, animal models, and humans	Iron chelator. Antioxidant properties. Improved short- and long-term outcomes after intracerebral hemorrhage.	Phase 2, randomized Parallel assignment Quadruple blind NCT02175225[d] NCT00777140[e]	[114]
Stroke	Mitochondrial transplantation	*In vitro*, animal models, and humans	Improvement of mitochondrial functions. No cardiovascular adverse effect, extracted mitochondria are active.	Single group assignment Open label NCT04998357[f]	[115,116]
CCM	Propranolol	*In vitro*, animal models, and humans	Ameliorate mitochondrial function. Decrease CCM lesions and vascular permeability.	Phase 2, randomized Parallel assignment Single blind NCT03589014[g]	[117]
AVMs	Sirolimus or everolimus (MTOR inhibitors)	*In vitro*, animal models, and humans	Mitochondrial function activator. Antivascular properties.	Phase 2 Single group assignment Open label NCT02042326[h]	[118]
ICAS	Recaticimab (PCSK9 inhibitor)	*In vitro*, animal models, and humans	Decreased ROS and mitochondrial fission. Reduced vulnerability of human carotid plaques.	Phase 3, randomized Parallel assignment Quadruple blind NCT07119918[i]	[86]

insertion at the same position appears protective [83]. Whether analogous mtDNA alterations contribute to ICAS by promoting mitochondrial instability, mtDNA leakage, inflammatory activation, or electron transport chain-dependent metabolic dysfunction remains to be clarified.

Functionally, mitochondrial dysfunction promotes vascular remodeling and luminal narrowing through multiple converging mechanisms. Sustained PTPC opening induces mitochondrial failure and VSMC death, which in ICAS favors apoptosis, cellular dysfunction, and fibrotic remodeling, thereby progressively narrowing the arterial lumen [84]. In contrast to IA, where VSMC loss weakens the vessel wall, in ICAS it contributes to plaque growth and arterial stiffening, underscoring the context-dependent consequences of mitochondrial stress. PTPC activation thus emerges as a shared mechanistic axis across distinct cerebrovascular pathologies, with divergent structural outcomes.

Another mitochondrial regulatory axis relevant to intracranial and carotid stenosis involves the proprotein convertase subtilisin/kexin type 9 (PCSK9), which links lipid dysregulation to vascular mitochondrial injury. Gain-of-function mutations enhance PCSK9 binding to low-density lipoprotein (LDL) receptors, promoting their lysosomal degradation and reducing hepatic LDL-cholesterol clearance, thereby accelerating atherogenesis [85]. Beyond its systemic lipid effects, PCSK9 directly impairs vascular cell viability by activating caspase-3, downregulating the antiapoptotic protein BCL-2, enhancing mitochondrial ROS generation, and suppressing respiratory complex I activity [86]. PCSK9 also induces mitochondrial fragmentation via p38 mitogen-activated protein kinase (MAPK)-dependent phosphorylation of DRP1 [86] (Figure 3). Notably, pharmacological inhibition of DRP1 with Mdivi-1 restores mitochondrial membrane potential, reduces VSMC death, and attenuates atherosclerotic remodeling in preclinical models [87]. In parallel, PCSK9-induced mitophagy, although initially adaptive [88], may become maladaptive when excessive (Box 1), leading to depletion of mitochondrial reserves and metabolic impairment. Together, these findings suggest that dysregulation of mitochondrial dynamics and quality control contributes to PCSK9-driven vascular pathology in ICAS.

Arteriovenous malformations

AVMs arise from profound endothelial dysregulation and defective interactions with pericytes and smooth muscle cells, producing structurally fragile, high-flow shunts [89]. Although mitochondrial mechanisms have been only marginally investigated in this context, early findings implicate mitochondrial stress and metabolic imbalance in endothelial instability and abnormal angiogenic behavior. Endothelial deletion of key mitochondrial genes, such as the transcription factor A, mitochondrial (TFAM), the complex IV assembly factor COX10, and the antioxidant enzyme thioredoxin-2 (TRX2), triggers metabolic collapse in the retina, producing microaneurysms and direct arteriovenous shunts typical of retinal AVMs [90]. This mitochondrial stress activates the transforming growth factor beta (TGFβ)–activin receptor-like kinase 5 (ALK5)–SMAD family member 2 (SMAD2) pathway, impairing endothelial proliferation and sprouting (Figure 3); conversely, ALK5 inhibition or SMAD2 loss rescues the vascular phenotype, identifying this axis

Notes to Table 1:
[a]https://clinicaltrials.gov/study/NCT01527240?cond=NCT01527240&rank=1
[b]https://clinicaltrials.gov/study/NCT06930638?term=NCT06930638&rank=1
[c]https://clinicaltrials.gov/study/NCT05857046?cond=NCT05857046&rank=1
[d]https://clinicaltrials.gov/study/NCT02175225?term=NCT02175225&rank=1
[e]https://clinicaltrials.gov/study/NCT00777140?term=NCT00777140&rank=1
[f]https://clinicaltrials.gov/study/NCT04998357?term=NCT04998357&rank=1
[g]https://clinicaltrials.gov/study/NCT03589014?term=NCT03589014&rank=1
[h]https://clinicaltrials.gov/study/NCT02042326?term=NCT02042326&rank=1
[i]https://clinicaltrials.gov/study/NCT07119918?term=NCT07119918&rank=1

as a potential therapeutic target in the retina [90]. Whether similar mechanisms operate in cerebral AVMs, however, remains unknown. In this context, using a rat AVM model that recapitulates key vascular features of cerebral AVMs, ultrastructural analyses revealed swollen mitochondria, disrupted cristae, and membrane damage in endothelial cells of arterialized veins—changes absent in control veins. Although these observations derive from extracerebral AVM tissue, they suggest that mitochondrial dysfunction impairs endothelial OXPHOS and contributes to the aberrant angiogenic phenotype, including elevated vascular endothelial growth factor (VEGF) secretion [91].

Endothelial metabolic reprogramming is increasingly recognized as a hallmark of arteriovenous malformations (AVMs) in **hereditary hemorrhagic telangiectasia (HHT)**. Accelerated cell cycle progression in both preclinical models and patient-derived specimens is associated with the upregulation of genes controlling glycolysis and mitochondrial energy production [92], likely supporting the heightened energetic demands of early AVM formation. These observations highlight a close coupling between endothelial cell cycle regulation and mitochondrial bioenergetics that may contribute to AVM pathogenesis in HHT.

Importantly, metabolic dysfunction within AVMs extends beyond the endothelium and affects additional cellular components of the lesion. In brain AVMs resulting from endothelial *RBPJ* deletion, central nervous system macrophages exhibit altered metabolic profiles. Specifically, increased expression of glutamine and glucose transporters (*SNAT1* and *GLUT3*) indicates a shift toward alternative energy substrates under inflammatory and metabolic stress (Figure 3). Interestingly, the microglia-enriched glucose transporter GLUT5 remains unchanged, highlighting a selective pattern of metabolic rewiring in the AVM microenvironment [93]. Collectively, these observations suggest that mitochondrial dysfunction in both endothelial and immune compartments contributes to impaired vascular stability and energy homeostasis in AVMs.

Cerebral cavernous malformations

CCMs are vascular lesions composed of dilated capillary-like vessels lacking normal structural support, such as smooth muscle or intervening neural tissue [94]. Unlike AVMs, CCMs are often low-flow and clinically silent lesions but can cause seizures, hemorrhages, or focal neurological deficits [94].

Recent studies suggest that mitochondrial dysfunction contributes to CCM pathogenesis, particularly through oxidative stress and endothelial cell dysregulation. Loss-of-function mutations in each of the genes associated with CCM, that is, cerebral cavernous malformations 1 protein [CCM1, also known as Krev interaction trapped protein 1 (KRIT1)], CCM2, and CCM3 (PDCD10), disrupt endothelial homeostasis and result in multiple CCM lesions. Among these, KRIT1 deficiency has been most strongly linked to altered mitochondrial function. *In vitro* studies have shown that loss of KRIT1 leads to increased ROS production and consequent mitochondrial derangements, such as loss of membrane potential, reduced Ca^{2+} entry, and low ATP production [95]. Such oxidative damage could be related, at least in part, to downregulation of the mitochondrial antioxidant systems, especially superoxide dismutase 2 (SOD2) [95] (Figure 3). Treatment with the ROS scavenger Tempol strongly reduces lesion burden and restores redox balance in a mouse model of CCM [96], supporting a role for oxidative stress modulation in limiting CCM lesion development. Importantly, deletion of all three autophagy-related genes results in a strong inhibition of the autophagic process, mainly due to aberrant activation of the mechanistic target of rapamycin kinase (MTOR) pathway [97], which could contribute to oxidative stress and endothelial damage by favoring the accumulation of defective

Clinician's corner

Mitochondrial dysfunction represents a shared pathophysiological vulnerability across cerebrovascular diseases, including ischemic stroke, intracranial aneurysms, arteriovenous malformations, intracranial atherosclerotic disease, and cerebral cavernous malformations. In these conditions, impaired mitochondrial bioenergetics and redox signaling influence endothelial stability, neurovascular coupling, and tissue tolerance to ischemic or hemorrhagic stress.

In acute ischemic stroke, mitochondrial dysfunction is a compelling biological target but a difficult therapeutic one. Mitochondrial injury develops within minutes to hours after vessel occlusion and reperfusion, often preceding clinical presentation and limiting opportunities for effective intervention. As a result, mitochondrial-targeted strategies have shown limited translational success when applied indiscriminately in acute stroke settings.

By contrast, several nonacute cerebrovascular conditions provide a more controlled peri-procedural window. In intracranial aneurysms, arteriovenous malformations, and intracranial atherosclerotic stenosis, surgical or endovascular interventions involve predictable, time-limited mitochondrial stress related to transient ischemia, reperfusion, or endothelial injury. These settings may represent a more feasible context for testing mitochondrial-modulating therapies as adjuncts to established procedural treatments.

Across cerebrovascular disorders, mitochondrial-directed approaches are unlikely to replace current therapies but may modify secondary injury. Their potential clinical value lies in reducing peri-procedural vulnerability, limiting delayed tissue damage, and improving recovery when integrated with revascularization, embolization, or vascular reconstruction strategies.

Mitochondrial transplantation represents an emerging and highly experimental strategy. While preclinical studies suggest that exogenous mitochondria can restore bioenergetic capacity in

mitochondria (Figure 3). In line with this notion, the use of pharmacological MTOR inhibitors (i.e., sirolimus) has been proposed as a therapeutic approach for CCM [98–100], although its efficacy may be restricted to specific subsets of sporadic CCMs [101,102].

CCM3 mutations are linked to more aggressive clinical phenotypes [103]. Importantly, transcriptomic analysis of both human and mouse CCM lesions reveals a unique profile for CCM3 that involves dysregulation of some mitochondrial genes, including *ALDH4A1*, which encodes an enzyme that supports proline metabolism and preserves mitochondrial redox homeostasis, and the key regulator of mitochondrial dynamics, *DNM1L* (encoding DRP1) [104]. Accordingly, endothelial cells depleted of *CCM3* exhibit multiple mitochondrial alterations, including morphological defects mainly driven by Krüppel-like factor 4 (KLF4) [105,106] (Figure 3). However, whether these mitochondrial abnormalities directly contribute to the more severe clinical phenotype associated with *CCM3* mutations remains to be established.

injured tissues, major challenges remain regarding delivery, safety, durability, and patient selection. At present, mitochondrial transplantation should be viewed as a future-oriented concept informing long-term therapeutic innovation rather than near-term clinical practice.

Mitochondria-targeted therapeutic strategies and clinical trials in cerebrovascular disease

Although specific mitochondrial alterations represent distinctive hallmarks of several cerebrovascular diseases and emerge as credible targets for the development of therapeutic strategies, many critical issues remain to be addressed (see Outstanding questions), and much of the available evidence is still at the preclinical stage, with actual clinical implications yet to be clearly defined. For example, the DRP1 inhibitor Mdivi-1 shows consistent neuroprotective effects in preclinical stroke models (as mentioned previously), but current evidence remains insufficient to justify clinical translation, mainly because of concerns related to target specificity [107] or limited brain bioavailability [108]. Along similar lines, a Phase 2 trial of CsA reported only modest benefits in selected patient subgroups, largely due to neurotoxicity and poor BBB permeability [109], while the MCUc inhibitor Ru265 failed to progress to clinical evaluation because of safety concerns, including convulsions observed in mouse models [46]. In this context, the alkaloid berberine has recently been shown to limit mitochondrial Ca^{2+} entry by selectively targeting the MCUc [110], and it displays a favorable safety profile, high BBB penetration, and robust efficacy in preclinical models [111]. Accordingly, berberine is currently being evaluated in a Phase 4 clinical trial in individuals with high cardiometabolic risk (NCT05749874), supporting its feasibility for clinical repurposing. Other bioactive compounds with antioxidant or cytoprotective properties, including MitoQ, melatonin, and the ferroptosis inhibitor deferoxamine mesylate, are currently under clinical evaluation in ischemic stroke (Table 1).

Therapeutic translation is also being explored in other cerebrovascular diseases. In CCMs and AVMs, propranolol and sirolimus, respectively, have shown beneficial clinical effects in early-phase trials. Notably, both compounds have been reported to improve mitochondrial function in preclinical settings [117,118]; however, whether these mitochondrial effects directly contribute to their clinical efficacy in these contexts remains premature to conclude. In parallel, ongoing clinical investigation in ICAS includes a Phase 3 trial of the PCSK9 inhibitor recaticimab, although broader clinical validation and long-term safety assessments are still required.

Despite the growing number of mitochondrial-targeted pharmacological strategies, several conceptual and technical bottlenecks continue to limit translational advances. These include the difficulty of achieving cell type-specific mitochondrial profiling within the neurovascular unit, the challenge of distinguishing causal mitochondrial alterations from secondary metabolic adaptations, and the limited availability of robust *in vivo* tools to monitor mitochondrial dynamics and redox signaling in real time.

Beyond pharmacological approaches targeting mitochondrial pathways, emerging evidence indicates that horizontal mitochondrial transfer between neurons and glial cells might emerge as a distinct and potentially complementary therapeutic avenue within the neurovascular unit, thereby reflecting an endogenous compensatory response to mitochondrial dysfunction. In the cerebrovascular system, mitochondrial transfer has been primarily characterized in stroke models, where both astrocytes and neurons actively exchange organelles. Following transient focal cerebral ischemia, astrocyte-derived functional mitochondria can be internalized by neurons, promoting neuronal survival [119], whereas damaged mitochondria released by stressed neurons are taken up by astrocytes, triggering enhanced mitochondrial biogenesis and metabolic reprogramming [120]. These observations support the concept that promoting mitochondrial transfer may represent a cytoprotective mechanism capable of restoring mitochondrial function and reinforcing glial-neuronal metabolic coupling in injured brain regions. Consistent with this view, mitochondrial transplantation has recently emerged as a cutting-edge therapeutic approach in ischemic stroke. Intra-arterial delivery of autologous mitochondria has been shown to reduce infarct size and improve cellular viability by increasing ATP production in preclinical models [115], and initial clinical evidence indicates that autologous mitochondrial transplantation can be performed safely in ischemic patients, with preserved mitochondrial purity and function [116]. Thus, rethinking mitochondria not only as intracellular targets but also as transferable therapeutic units may redefine future strategies for cerebrovascular disease treatment. However, this potential approach should be interpreted with caution, as the molecular determinants regulating mitochondrial transfer and acceptance within the cerebrovascular system remain only partially understood [121], and in certain contexts, such organelle exchange may also contribute to maladaptive cellular responses [122].

Concluding remarks and future perspectives

Mitochondrial dysfunction represents a central pathogenic mechanism across several cerebrovascular diseases and, therefore, emerges as a promising molecular target to mitigate the detrimental consequences of events such as stroke and aneurysm formation. However, despite encouraging preclinical evidence, clinical translation remains limited. One of the major bottlenecks lies in the scarcity of robust clinical evidence for many promising compounds that have shown efficacy in *in vitro* and animal models. In addition, limited brain bioavailability and potential off-target effects continue to represent important barriers to therapeutic development.

Overall, the evidence discussed in this review highlights mitochondria as a central molecular hub that directly or indirectly contributes to the onset and progression of cerebrovascular diseases. Accordingly, targeting mitochondrial dysfunction may represent a promising therapeutic strategy, although its clinical implementation will require improved drug delivery, a better mechanistic understanding, and more rigorous translational frameworks.

Outstanding questions

What are the main translational barriers preventing mitochondrial-targeted interventions from achieving consistent clinical benefits in cerebrovascular diseases, despite robust preclinical evidence?

How do timing, disease stage, and clinical context influence the therapeutic relevance of targeting mitochondrial permeability and redox signaling in acute versus nonacute cerebrovascular conditions?

How do distinct forms of regulated cell death intersect with mitochondrial dysfunction across different temporal stages of cerebrovascular diseases?

Which patient subgroups or procedural settings might be most suitable for testing mitochondrial-modulating therapies as adjuncts to existing surgical or endovascular treatments?

What technical, biological, and safety challenges must be overcome before mitochondrial transplantation can be realistically evaluated across different cerebrovascular diseases?

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The authors declare no competing interests.

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During the preparation of this work, the authors used ChatGPT 5.2 for proofreading and editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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