Focus on the role of mitochondria in NLRP3 inflammasome activation: A prospective target for the treatment of ischemic stroke (Review)

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Abstract. Post-ischemic neuroinflammation induced by the innate local immune response is a major pathophysiological feature of cerebral ischemic stroke, which remains the leading cause of mortality and disability worldwide. NLR family pyrin domain containing (NLRP)3 inflammasome crucially mediates post-ischemic inflammatory responses via its priming, activation and interleukin-1β release during hypoxic-ischemic brain damage. Mitochondrial dysfunctions are among the main hallmarks of several brain diseases, including ischemic stroke. In the present review, focus was addressed on the role of mitochondria in cerebral ischemic stroke while keeping NLRP3 inflammasome as a link. Under ischemia and hypoxia, mitochondria are capable of controlling NLRP3 inflammasome-mediated neuroinflammation through mitochondrial released contents, mitochondrial localization and mitochondrial related proteins. Thus, inflammasome and mitochondria may be attractive targets to treat ischemic stroke as well as the several drugs that target the process of mitochondrial function to treat cerebral ischemic stroke. At present, certain drugs have already been studied in clinical trials.

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Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD; ARE, antioxidant response element; ANT1, adenine nucleotide translocase 1; DAMP, damage-associated molecular pattern; ER, endoplasmic reticulum; IL-1β, interleukin-1β; K-ATP, ATP-sensitive potassium channels; LRR, leucine rich repeat; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; MCU, mitochondrial $Ca2^{+}$ uniporter; MFN, mitofusin; MAM, mitochondria-associated ER membranes; mtROS, mitochondrial ROS; MRC, mitochondrial respiratory chain; NAD^{+}, nicotinamide adenine dinucleotide; Nec-1, necrostatin-1; Nrf2, nuclear factor E2-related factor-2; OXPHOS, oxidative phosphorylation; OGD/R, oxygen-glucose deprivation/reoxygenation; PAMP, pathogen-associated molecular pattern; PTM, post-translational modification; RIPK1, receptor-interacting protein kinase 1; ROS, reactive oxygen species; SHP2, Src homology 2 domain-containing tyrosine phosphatase-2; TXNIP, thioredoxin interacting protein; TRX, thioredoxin; TRPM2, transient receptor potential melastain 2; tMCAO, transient middle cerebral artery occlusion

Key words: ischemic stroke, mitochondria, neuroinflammation, NLR family pyrin domain containing 3 inflammasome, treatment

Contents

1. Introduction

Ischemic stroke is a common cause of disability, normally manifested as long-term neurological impairment, and even death (1,2). The pathogenesis of ischemic stroke is mainly caused by atherothrombosis at large cervical or intracranial arteries or by occlusion of cardio-embolus (3), which results in insufficient oxygen and glucose delivery to meet the requirement of cellular respiration (4). To date, the approved therapies of ischemic stroke are intravenous thrombolysis or thrombectomy (5), which can only be applied to a very small fraction of patients due to the narrow time window and strict indication criteria (6). As such, there is an urgent need to develop novel and alternative treatment strategies to treat ischemic stroke.

Post-ischemic neuroinflammation is an important pathological hallmark that affects both the development and prognosis of ischemic stroke (7,8). Once the inflammatory cascade is turned on, it aggravates neuron dysfunction and induces breakdown of blood brain barrier, brain edema and ultimately neuron death (9). Inflammasomes are intracellular multiprotein complexes that drive the activation of inflammatory responses. Among all types of inflammasomes, such as NLR family pyrin domain containing 1 (NLRP1), NLRP3, NLR family CARD domain-containing protein 4 (NLRC4), and absent in melanoma 2 (AIM2), NLRP3 is the most studied one, particularly in the central neural system (10). It was shown that NLRP3 inflammasome activation regulates inflammatory response and accelerates neuron damage (11), and it acts as a key intermediate of neuroinflammation during the progress of ischemic stroke (12). Thus, inhibition of NLRP3 inflammasome activation may be applied as a novel treatment strategy for ischemic stroke (13).

Alternatively, mitochondrion is an organelle that plays roles in energy conversion and metabolism, and its dysfunction is the crucial pathophysiological change in ischemic stroke due to oxygen-glucose deprivation (14). It was found that a few studies have confirmed that NLRC4 (15), NLRP1 (16) and AIM2 (17) can promote cerebral ischemic injury, but there is no evidence that mitochondria can affect the pathological process of cerebral ischemia through them. Previous studies revealed that mitochondrial dysfunction is a vital event during the NLPR3 inflammasome activation (18-20). However, the role of NLRP3 inflammasome in sensing mitochondrial damage and how mitochondria trigger NLRP3 activation in ischemic stroke is to be elucidated (21). The present review focused on the role of mitochondria in NLRP3 inflammasome activation under ischemic stroke and described the currently used drugs and potential treatment targets for ischemic stroke.

2. Pathophysiological changes of mitochondria in ischemic stroke

The most sensitive organ suffering from ischemia and hypoxia is the brain (22), which depends on continuous delivery of oxygen and nutrients to maintain its function (23). Adult brain accounts for 20% of all the oxygen consumed by the whole body, with merely 2% of the total body weight (24). Given the high-energy demanding nature of neurons in the brain, it is essential that the mitochondrial pool remains healthy and provides a continuous and efficient supply of energy (25). Mitochondria produce most ATP production through mitochondrial respiratory chain (MRC) and oxidative phosphorylation (OXPHOS). However, mitochondria are very sensitive to ischemia and hypoxia (26); under these circumstances, they undergo significant alterations, including Ca^{2+} influx, mitochondrial permeability transition pore (mPTP) opening, reactive oxygen species (ROS) generation, DNA damage and mutation, unbalanced mitochondrial dynamics, and aberrant mitochondrial position (27-29). These changes in mitochondria are termed as mitochondrial dysfunction, which is strongly implicated in patients and multiple animal models with ischemic stroke (30-34).

During ischemic stroke, ischemia and hypoxia reduce ATP production and lead to dysfunction of the Na^+/K^+ ATPase pump (35). Within min following the onset of cerebral ischemia, ATP depletion deactivates the sodium-potassium pump and then excessive glutamate is released into extracellular fluid (36). Glutamate, as the main excitatory neurotransmitter in the central nervous system, is essential to multiple functions of neurons by binding to different types of receptors including N-methyl-d-aspartate receptor and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (37). Under ischemia-hypoxia condition, the high level of extracellular glutamate induces massive calcium influx, which further aggravates mitochondrial calcium overload (38). Elevated mitochondrial calcium launches a series of events ranging from mPTP opening and dissipation of $\Delta\Psi m$ to excessive ROS production, leading to neuroinflammation and eventually neuronal death (Fig. 1) (28). While Inhibition of the heat shock 75-kDa glucose-regulated protein was able to effectively ameliorate mitochondrial calcium overload and alleviate the ischemic stroke (39).

Meanwhile, the decreased ATP depletes nicotinamide adenine dinucleotide (NAD^+), whose bioenergy state is a critical determinant for neuronal survival under excitotoxicity and ischemia (40). The reduced NAD^+ motivates mitochondria to the vicinity of endoplasmic reticulum (ER) to form mitochondria-associated ER membranes (MAMs) (41). The diverse drugs or compounds with clear anti-stroke effects were revealed to reduce or partially reverse neuronal damage through inhibition of MAM-related proteins following ischemic stroke (42,43). Moreover, certain MAM-related proteins join mPTP to regulate its opening (44), which is an important marker of cerebral cell death during ischemia/reperfusion. Once ischemia/reperfusion injury promotes mPTP opening, mitochondrial ROS (mtROS), mitochondrial DNA (mtDNA) and cardiolipin inside the mitochondria are released into the cytoplasm, where they act as danger signals when recognized by innate immune receptors to exacerbate ischemia damage (45).

Besides energy production, mitochondria also generate a small amount of ROS, which induces oxidative damage (46). Increased ROS was generated during cerebral ischemia, particularly during reperfusion by disrupting mitochondrial electron transport (47,48). The broken mitochondria produce large amounts of ROS, which in turn affect the function of adjacent mitochondria. Since mitochondria are both the sources of ROS production and the targets of ROS, oxidant-induced mitochondrial dysfunction forms a 'vicious cycle' in patients with ischemic stroke (49,50). Furthermore, the ROS release results in oxidation and mutation of mtDNA, release of mitochondrial proteins and impaired mitophagy as shown in rat model of middle cerebral artery occlusion (MCAO). Moreover, the accumulation of ROS promotes neuroinflammation and neuron apoptosis after oxygen-glucose deprivation/reoxygenation (OGD/R) (51).

In addition to mitochondrial function, changes in mitochondrial structure play an important role in the progress of ischemic stroke. Mitochondria are highly dynamic organelles to regulate their size, form and mtDNA integrity via continuous fission, fusion and mitophagy (52). When neurons undergo ischemia, mitochondrial fission and fusion are transitory to maintain its structure integrity and function. However, under the circumstance of large amount of ROS production (53) and

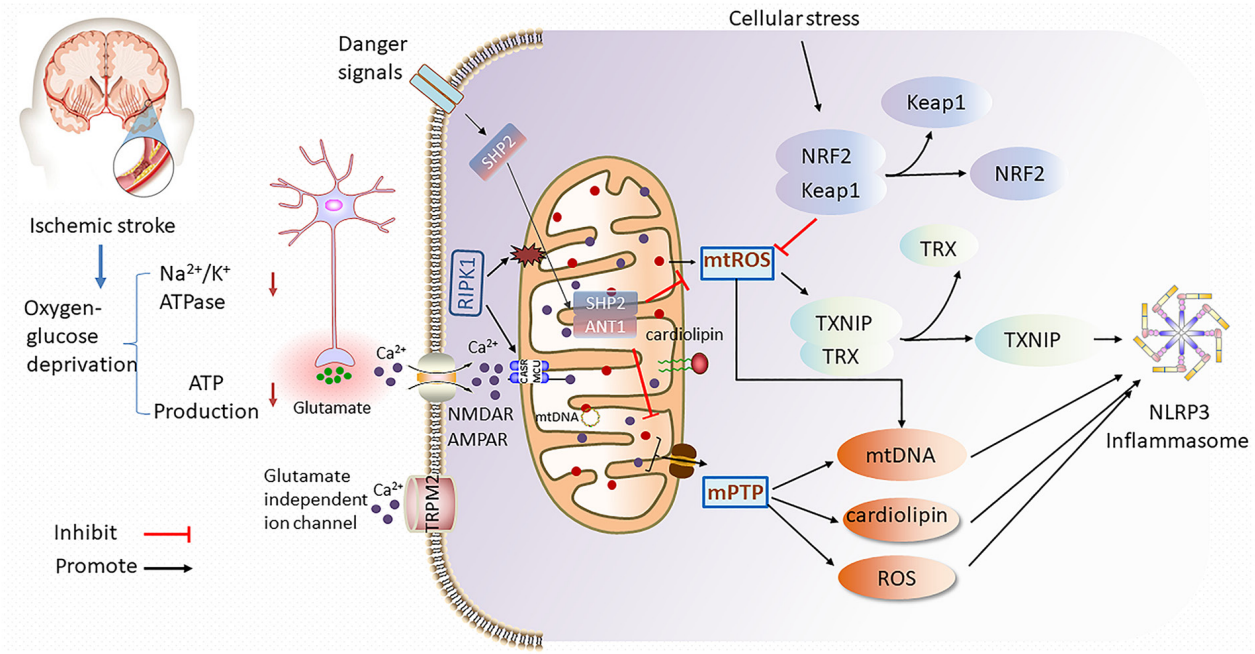

Figure 1. Mitochondria play a pivotal role in the pathological process upon ischemic insult. ATP depletion due to OGD leads to Na^+/K^+ ATPase pump dysfunction. This causes the depolarization of neuronal membrane to release excessive glutamate. In turn, glutamate receptors, such as NMDA and AMPA, are over activated, resulting in calcium influx into neurons. TRPM2 channel, which is a glutamate-independent ion channel, also leads to intracellular Ca^{2+} calcium overload which induces mtROS release. Finally, ROS release and mitochondrial dysfunction ensures to initiate inflammation. The production of ROS leads to the dissociation of TXNIP from TRX to active NLRP3 inflammation. RIPK1 interacts with MCU to upregulate mitochondrial Ca^{2+} uptake and disrupts the mitochondrial membrane integrity. Furthermore, ischemia triggers the depolarization of $\Delta\Psi m$ and induction of mPTP, which leads to the production of mitochondrial DAMPs (such as cardiolipin and mtDNA). Under the stimulation of risk factors, such as lipopolysaccharide and nigericin, SHP2 enters cells and binds to ANT1, thus stabilizing mPTPs and inhibiting the release of mtROS and mtDNA. The dissociation of Nrf2 from Keap1 can inhibit mtROS release. These can cause the activation of NLRP3 inflammasome and contribute to tissue damage following ischemic stroke injury. OGD, oxygen-glucose deprivation; NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate; mtROS, mitochondrial ROS; ROS, reactive oxygen species; TXNIP, thioredoxin interacting protein; TRX, thioredoxin; NLRP3, NLR family pyrin domain containing 3; RIPK1, necrosome-containing receptor-interacting protein kinase 1; MCU, mitochondrial Ca2+ uniporter; mPTP, mitochondrial permeability transition pore; DAMP, damage-associated molecular pattern; SHP2, Src homology 2 domain-containing tyrosine phosphatase-2; ANT1, adenine nucleotide transferase 1; mtDNA mitochondrial DNA.

mtDNA damage (54), mitochondria are divided excessively, resulting in mitochondrial dysfunction (55). Thus, mitochondrial fission occurs as an upstream and early event in brain cell death following ischemia (56,57).

Furthermore, mutation mtDNA genes is correlated mitochondrial dysfunction with genomic instability. mtDNA is markedly more prone to mutations than nuclear DNA (58). Particularly, the frequency of mtDNA mutations was found to be significantly higher in the brain of patients with ischemic stroke, and numerous of these mutations resulted in an alteration of amino acid therefore structure of protein (34). The vulnerability of mtDNA to mutation is due to its lacking of high-fidelity repair processes, the high-copy-number of mtDNA within each cell, and the close proximity to ROS-generating machinery (59). In a word, mutation of gene-encoded subunits in mtDNA results in more ROS generation, which turns mtDNA more susceptible to mutation.

3. NLRP3 inflammasome-mediated neuroinflammation in ischemic stroke

Neuroinflammation in ischemic stroke. Upon stroke attack, the interruption and reperfusion of blood flow in the brain tissue trigger the infiltration of inflammatory cells to induce neuronal death (60). Neuroinflammation is a primary pathological event involved in the process of ischemic injury and repair (61). In response to injury in the brain, neuroinflammation occurs in various cells, including neurons, microglia and astrocytes (62). In the acute phase, the damaged neurons and resident immune cells secrete inflammatory mediators and activate microglia, which are the first line of defense in the nervous system (63) that produce more inflammatory factors (62,64). Additionally, astrocytes that are activated by ischemia mediate inflammatory response to aggravate ischemic injury. However, they also limit the spread of inflammation by inhibiting excitotoxicity and secreting neurotrophic factors (65,66). Interestingly, NLRP3 inflammasome was found to play a key role in driving neuroinflammation in these cells during acute ischemic stroke, and early blockade of NLRP3 protects neurons from ischemia-reperfusion injury by mitigating inflammation (67).

The composition and activation of the NLRP3 inflammasome. NLRP3 inflammasome is the most widely described inflammatory complex, which is composed of NLRP3 as its receptor, apoptosis-associated speck-like protein containing a CARD (ASC) as its adaptor, and caspase-1 as its effector. Activation of NLRP3 inflammasome includes two steps, namely, priming and activation (68). The priming step is the recognition of pathogen-associated molecular pattern (PAMP) or damage-associated molecular pattern (DAMP) via pattern recognition

receptors (PRRs). Transcription and post-translational modification (PTM) of NLRP3 inflammasome promote the transcription of NLRP3 and the precursor of caspase-1, interleukin (IL)-1β and IL-18 (69). The priming of NLRP3 inflammasome not only provides material for NLRP3 inflammasome activation, but also allows NLRP3 and ASC to form the inflammasome assembly (70) or to protect them from degradation (71) through various PTM including ubiquitylation, deubiquitylation and phosphorylation. Then, the activation step is required to initiate the NLRP3 inflammasome assembly and subsequent activation. Generally, NLRP3 is oligomerized via its NACHT domains once activated (72). NLRP3 trimerization rather than dimerization is necessary for the inflammasome activation (73). Subsequently, activated NLRP3 interacts and recruits the adaptor molecule ASC via PYD-PYD interaction (74). The polymerized ASC further recruits the enzyme caspase-1 through CARD-CARD interactions to initiate autocatalytic cleavage of caspase-1 (75). Notably, ASC oligomerization is a key step in caspase-1 activation and caspase-1-dependent pyrophosphorylation upon NLRP3 stimulation (76). Once activated, caspase-1 cleaves the inactive pro-IL-1β and pro-IL-18 to release their active form of cytokines IL-1β and IL-18 to induce neuroinflammation and pyroptosis (77).

NLRP3 inflammasome in ischemic stroke. NLRP3 inflammasome is generally expressed in immune organs and cells, and is also expressed in the central nervous system (78,79). Liu *et al* (80) found that NLRP3 was activated in the microglia of ischemia-reperfusion injury rat model (81). Moreover, recent study suggested that NLRP3 was also expressed in the endothelial cells, neurons, and astrocytes of ischemic brain (82). It was demonstrated that NLRP3 inflammasome was firstly activated in microglia and then expressed in microvascular endothelial cells and neurons of transient MCAO (tMCAO) rat model (83).

Elevated levels of enlarged infarct size, neurological function and brain infarct volume were observed in MCAO rats with activation of NLRP3 inflammasome compared with sham rats (84). Furthermore, IL-1β and IL-18 levels were increased in the ipsilateral brain of ischemia-reperfusion mice model as well as in the postmortem ipsilateral brain of patients with stroke (79). The NLRP3 inhibitor MCC95 significantly reduced the infarct volume in a dose-dependent manner, the expression of different pro-inflammatory cytokines and NLRP3 inflammasome components, indicating its neuroprotective effect in the MCAO mice (85). Furthermore, elevated expression of NLRP3, caspase-1, ASC and IL-1β were present in a murine model of cerebral ischemia, while caspase-1 inhibition by VX765 prevented these changes and neuronal death. In summary, NLRP3 inflammasome exerts essential functions in the pathogenesis of ischemic stroke.

4. Mitochondria regulate NLRP3 inflammasome activation during ischemic stroke

Mitochondria regulate NLRP3 inflammasome activation under cerebral ischemia in bidirectional mode. Mitochondria are involved in the initiation and activation of NLRP3 inflammasome, leading to neuroinflammation and pyroptotic cell death (86). On one hand, the opening of mPTPs in damaged mitochondria release DAMPs, such as ATP, mtROS, cardiolipin and mtDNA, which are common causes for NLRP3 inflammasome activation (87). The localization of mitochondrial and its membrane-associated proteins also takes positive participation in activation of NLRP3 inflammasome during cerebral ischemic damage. On the other hand, active mitophagy and fractional mitochondrial-related proteins such as Src homology 2 domain-containing tyrosine phosphatase 2 (SHP2), mitofusin 2 (Mfn2) and nuclear factor E2-related factor-2 (Nrf2) negatively regulate the NLRP3 inflammasome expression to protect brain from ischemic injury (88) (Fig. 1).

The positive role of mitochondria in NLRP3 inflammasome activation. Mitochondrial-released contents. mtROS. Dysfunctional mitochondria produce large amounts of mtROS by transferring electrons from the MRC to molecular oxygen to form mtROS (77). MtROS are important in NLRP3 priming and activation. It was revealed that mtROS regulates NLRP3 initiation earlier than activation by upregulating its transcription (89). As a non-transcriptional priming signal, deubiquitination of NLRP3 depends on mtROS generation (90). Elimination of mtROS inhibits NLRP3 deubiquitination, in response to lipopolysaccharide stimulation (91,92). By contrast, mtROS induces NLRP3-dependent lysosomal damage and inflammasome activation, and promotes macrophages pyroptosis by inducing Gasdermin D oxidation (93), which can be reversed by scavenging mtROS (94).

Next, high concentrations of mtROS results in NLRP3 activation and IL-1β production (92). Furthermore, increased mtROS induced by ischemia-reperfusion injury leads to release IL-1β, IL-18 and caspase-1 by cleaving their precursors (95). Conversely, inhibiting mtROS formation or eliminating mtROS by antioxidants strongly impairs the activation of NLRP3 inflammasome and IL-1β release (96,97). It was reported that mtROS-NLRP3 signaling is activated in BV2 cells after OGD/R for 24 h. Inhibition of mtROS release suppresses NLRP3 activation and alleviates NLRP3-mediating damage in microglia of ischemia-reperfusion rats (33).

Cardiolipin. Apart from mtROS, the opening of mPTPs releases other mitochondria-related DAMPs like mtDNA and mitochondrial lipids during ischemic stroke (98). Among the different mitochondrial lipids, cardiolipin is an anionic phospholipid that localizes at the inner mitochondrial membrane and facilitates OXPHOS in mitochondria (99). Cardiolipin oxidation and hydrolysis are a key mechanism of ischemia-reperfusion-induced brain injury (100). Nowadays, cardiolipin is reported to be effective for triggering the activation of NLRP3 inflammasome (101) after acute ischemia (102). On one hand, cardiolipin directly interacts with both the N-terminal leucine-rich repeat (LRR) of NLRP3 and full-length of caspase-1 of NLRP3 inflammasome (86,103). On the other hand, NLRP3 is tethered to mitochondria by cardiolipin in an mTROs-dependent manner and is thereby activated (104). Either interference with cardiolipin synthesis or knockdown of cardiolipin specifically inhibits NLRP3 inflammasome activation (78).

mtDNA. mtDNA was recognized as one of the endogenous DAMPs, which is released from damaged mitochondria into

the cytoplasm to activate NLRP3 inflammasome and induce pyroptosis. It was shown that mtDNA was indispensable for NLRP3 activation by mtROS after ischemia-reperfusion (105,106). In response to various NLRP3 activators, mtDNA is rapidly released into cytoplasm to be oxidized to oxidized mtDNA (ox-mtDNA). Then, ox-mtDNA specifically localizes to NLRP3 (106), and directly binds to NLRP3 to trigger NLRP3 inflammasome activation (107). It was identified that NLRP3 inflammasome is over-activated in aged individuals, due to increased production of mtROS and/or mtDNA (108). High level of mtDNA induces the interaction of ASC with NLRP3 and pro-caspase-1 and promotes neuronal pyroptosis in the hippocampus of rats with incomplete ischemia-reperfusion injury (109). Correspondingly, repairing mtDNA oxidative damage inhibits NLRP3 activation and reduces reperfusion-associated ischemic brain injury (110). These results imply that mtDNA interacts with NLRP3 inflammasome to form positive feedback during the development of ischemic stroke.

Mitochondrial localization. MAMs. ER-mitochondrial contact is mediated by a specific membrane structure, known as MAM, which plays key roles in material transfer and signal transduction, including Ca^{2+} signaling (111,112). Notably, increased MAM aggravates mitochondrial dysfunction and enhances ROS production (113). In addition, MAM has overarching roles in innate immune system. When NLRP3 localizes at ER membrane, it is in the resting state. By contrast, when it relocates to MAM, it switches to activated state and functions in detecting ROS production from damaged mitochondria (114). Recruitment of NLRP3 to mitochondria enhances the ability of mtROS to activate NLRP3 inflammasome. ASC predominantly localized to the mitochondria, is transferred to MAM under the stimulation of NLRP3 activators. Furthermore, colocalization of ASC with MAM requires the presence of NLRP3 and is Ca^{2+} dependent (115). Notably, mitochondrial damage by NLRP3 inflammasome activators leads to the accumulation of NLRP3 and ASC in MAM (116). Ischemia-reperfusion injury increases the expression of MAM-related proteins, which accelerated signal communication with mitochondria through MAM in the male C57BL/6 mice (117). Silencing MAM-related protein p66Shc protects the integrity of blood-brain barrier, reduces infarct area, relieves the neurological deficit, and improves the survival rate of mice after MCAO (118). In a word, MAM is an ideal site for NLRP3 inflammasome activation and assembly which accelerates the development of ischemic stroke (119).

Microtubules. Generally, the movement of mitochondria in neurons is considered to be mediated by microtubules or microfilaments. Microtubules, which are formed by polymerization of α and β tubulins, are cell cytoskeleton to support intracellular transport between various organelles, particularly those involved in mitochondrial transport (120). Microtubules undergo various PTMs to take part in the transportation between mitochondria and ER, as well as in the subcellular localization of NLRP3 and ASC. Correspondingly, NLRP3 inflammasome activators induce mitochondrial transport to ER through the microtubule system, thereby facilitating the transfer of ASC from mitochondria to ER to combine with NLRP3 (121). A previous study found that the acetylation of microtubule α-tubulin is a necessary step for NLRP3 inflammasome activation (41) (Fig. 2). Moreover, NAD^+ is an endogenous small molecule that regulates the microtubules (122). NAD^+ caused by reduced ATP production moves mitochondria through microtubules, therefore promotes the assembly of NLRP3 inflammasome (41). Nicotinamide partially increases cellular NAD^+ levels and effectively protects neurons from ischemic damage (40).

Mitochondrial-related proteins

Thioredoxin interacting protein (TXNIP). TXNIP is an endogenous inhibitor of the thioredoxin (TRX) system and is expressed in nearly all cytoplasm and mitochondria (123). MtROS was revealed to promote the combination of NLRP3 with TXNIP which is a critical step that links oxidative stress to neuroinflammation (124,125). In response to mtROS release, TXNIP dissociates from TRX and translocates to MAM, to bind with NLRP3 and induces NLRP3 inflammasome activation (126). Inhibition of TRX expression interrupts the interaction between TRX and TXNIP, thus promoting the binding of TXNIP to NLRP3 and triggers the assembly and oligomerization of the NLRP3 inflammasome (127). In addition, TXNIP expression is upregulated in patients with stroke and rat model of cerebral ischemia (123,128). The inactivation of TXNIP relieves neurological deficits, cerebral infarction and edema from ischemic damage (123). Finally, TRX inhibitor downregulates the expression of TXNIP and suppresses NLRP3 inflammasome activation in astrocytes with OGD/R (80).

Ca^{2+} and its receptors. Ca^{2+} concentration increases either by Ca^{2+} influx from the extracellular space as triggered by neuronal activity or by Ca^{2+} outflux from the ER (129). Ca^{2+} accumulation is the determining factor of mPTP opening, which is an important marker of nerve cell death during ischemia, ensues by release of mitochondrial components that activate NLRP3 inflammasome (130). It has been revealed that NLRP3 receptors are activated by increased intracellular Ca^{2+} concentration *in vitro* and *in vivo* (131). Furthermore, when Ca^{2+} concentration in the cytoplasm increases, mitochondria uptake a large amount of Ca^{2+} through calcium-sensitive receptor (CASR) to activate the NLRP3 inflammasome. Consistently, knockdown of CASR reduces inflammasome activation. Moreover, a CASR agonist upregulates the expression of NLRP3, cleaved caspase-1, and IL-1β in the ipsilateral cortex of mice after stroke (132). Intriguingly, high intracellular Ca^{2+} concentration can also lead to Ca^{2+} influx to mitochondria through mitochondrial calcium uniporter (MCU), then loss of $\Delta\Psi m$, resulting in NLRP3 inflammasome activation and IL-1β secretion (133). Murakami *et al* (134) proposed that Ca^{2+} signaling is an intermediate step of NLRP3 inflammasome activation. Similarly, transient receptor potential melastain-2 (TRPM2) channel is a glutamate-independent ion channel. Under the condition of ischemia injury, TRPM2 channel can be activated and mediate the transport of Ca^{2+}, leading to intracellular calcium overload. Notably, intracellular calcium level further drives TRPM2 activity. In addition, TRPM2 promotes NLRP3 activation in OGD-induced neuronal injury, which was abolished by TRPM2 knockdown (135).

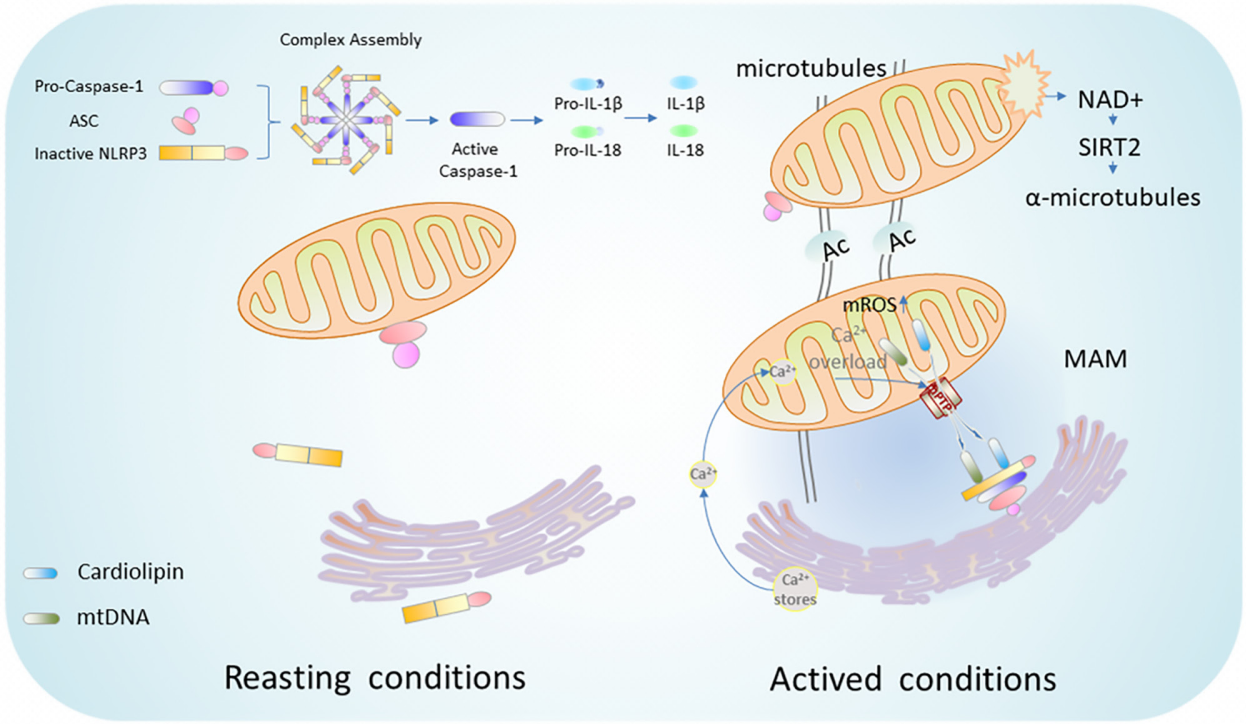

Figure 2. Mitochondrial transport promotes NLRP3 activation. Under physiological conditions, most NLRP3 localizes to the cytoplasm and ER, whereas ASC is localized to mitochondria. Once the mitochondria are damaged by NLRP3 inflammasome activator, the intracellular NAD^+ level is reduced. This is followed by the inactivation of the NAD^+-dependent deacetylase Sirt2, which ultimately leads to the accumulation of acetylated alpha-tubulin. It results in the redistribution of ASC from mitochondria and NLRP3 from ER to MAM. Moreover, MAM-mediated tight binding of ER to mitochondria depends on mitochondrial Ca^{2+} uptake which increases mtROS. Both Ca^{2+} and mtROS can open the mPTP. Thus, Ca^{2+} overload and production of mtROS contributes to the release of mitochondria-related factors such as mtDNA and cardiolipin, which ultimately activates the NLRP3 inflammasome. NLRP3, NLR family pyrin domain containing 3; ER, endoplasmic reticulum; ASC, apoptosis-associated speck-like protein containing a CARD; NAD, nicotinamide adenine dinucleotide; MAM, mitochondria-associated ER membrane; mtROS, mtROS, mitochondrial ROS.

Necrosome-containing receptor-interacting protein kinase 1 (RIPK1). RIPK1 is considered an essential regulator of apoptosis, necroptosis and inflammatory response. Under cerebral ischemia-hypoxia condition, RIPK1 induces necrotic apoptosis and neuroinflammation by destroying plasma membrane of endotheliocyte and microglia (136). Subsequently, released DAMPs from brain cells cause secondary inflammatory response, which aggravates ischemic damage (137,138). Upon being transported to out membrane of mitochondria, RIPK1 interacts with MCU to upregulate mitochondrial Ca^{2+} uptake, which leads to mtROS generation and NLRP3 activation (139). RIPK1 is upregulated in rat brain upon MCAO and localized to the microglia. Furthermore, RIPK1 triggers activation of NLRP3 inflammasome by disrupting the mitochondrial membrane integrity and by promoting mtROS release in ischemic microglia (140). As the first selective inhibitor, necrostatin-1 (Nec-1) significantly decreased RIPK1 phosphorylation in rat brain following ischemic stroke. Consistently, Nec-1 hindered IL-1β maturation in ischemic brains of rats (141).

Dynamin-related protein 1 (Drp1). Mitochondrial dynamics are regulated by specific proteins through mitochondrial fission and fusion (142) which play an important role in NLRP3 inflammasome assembly and activation (143). Mitochondrial fission is primarily contributed to Drp1 activation (144), which promotes mitochondrial Ca^{2+} uptake (145) to trigger NLRP3 inflammasome activation. Consistently, inhibition of Drp1-dependent mitochondrial fission protects neurons from ischemic stroke by preserving the activity of respiratory chain, reducing superoxide production and delaying Ca^{2+} dysregulation (146). Moreover, inhibition of Drp1 withholds NLRP3 inflammasome activation and protects mitochondrial integrity to exert its neuroprotective effects (147). A recent study showed that neuronal death was prevented in MCAO rat model by lowering Drp1 expression and NLRP3 signal transduction (148).

The negative role of mitochondria in NLRP3 inflammasome activation

Mitophagy. Following ischemia-reperfusion injury, the damaged mitochondria are removed by autophagy-related mechanism, which is known as mitophagy (149). Mitophagy is an important mechanism of mitochondrial renewal and metabolism which downregulates the number and controls quality of mitochondria, induces mitochondria to maintain dynamic homeostasis (150) and consequently reduces mitochondria-dependent neuronal cell death (151). In previous studies, it was identified that induction of mitophagy protects against cerebral ischemia-reperfusion injury by inhibiting NLRP3 inflammasome activation (149,152). Following ischemia-reperfusion, mitophagy increased locally reduces the neuroinflammatory response induced by NLRP3 inflammasome to relieve neurological deficits (153). Blockage of

mitophagy enhances the activation of the NLRP3 inflammasome (154). The damaged and dysfunctional mitochondria enhance NLRP3 inflammasome activation upon treatment with mitophagy inhibitors (116).

Mitochondrial transfer. Astrocytes (AS) are the most abundant glial cells in the central nervous system (155). When ischemic stroke occurs, AS provide energy support for injured neurons through the changes of its own bioenergy and mitochondrial dynamics (156). In addition, AS sense stress, transfer mitochondria as a 'help me' signal to adjacent injured neurons (157) and rescue damaged neurons from mitochondrial dysfunction to deal with stress (158). Concurrently, neurons also release damaged mitochondria and transfer them to as for endocytosis and degradation (159), so as to realize the recycling of mitochondria, making mitochondria crosstalk between healthy cells and damaged cells.

SHP2. SHP2 is a negative regulator of NLRP3 inflammasome activation (160). In response to NLRP3 inflammasome stimuli, SHP2 translocates to mitochondria and binds to adenine nucleotide transferase 1 (ANT1), which prevents the opening of mPTPs and the subsequent release of mtDNA and mtROS, thereby inhibiting NLRP3 inflammasome over-activation (160). In a focal cerebral ischemia model, ischemia-induced neuronal damage and death were significantly increased in nestin-SHP2-CS mice (SHP2 function was selectively removed from central nervous system) compared with wild-type mice. Additionally, transgenic mice that overexpress SHP2 are more sensitive to ischemia-induced brain damage (161).

Mfn2. Mfn2, a mitochondrial outer membrane protein, plays a pivotal part in mitochondrial fusion. It was reported that Mfn2 is downregulated while NLRP3 inflammasome and pyroptosis are activated in microglia and astrocytes of rats upon ischemia-reperfusion injury (162). Mfn2 overexpression attenuates free fatty acids induced mitochondrial damage, decreases mtROS production and inhibits NLRP3 inflammasome activation (163). Additionally, Mfn2 improves hypoxia induced neuronal apoptosis and prolongs the treatment time window of ischemic stroke by mitochondrial pathway (164).

Nrf2. Nrf2 is a well-known transcription factor that dissociates from Keap1 then translocates into the nucleus to initiate gene transcription via binding to antioxidant response element (ARE) during cellular stress conditions (165,166). The knockout of Nrf2 aggravates oxidative stress and inflammation (167). Nrf2 abates NLRP3 inflammasome activation by inhibiting the priming step to limit the assembly of NLRP3 inflammasome (96,168). Following cerebral ischemia-reperfusion, the activated Nrf2/ARE pathway inhibits ROS-induced NLRP3 inflammasome activation in BV2 microglia (169). Nrf2 knockout mice showed larger infarct size following ischemia-reperfusion, compared with that of control counterparts (170). Moreover, Nrf2 siRNA increased expressions of TXNIP, NLRP3, caspase-1 and IL-1β in brain of MCAO rats (171). Consequently, Nrf2 protects against NLRP3 inflammasome activation by regulating the TRX/TXNIP complex during cerebral ischemia-reperfusion injury (172).

5. Drugs that target mitochondria

Tissue plasminogen activator (tPA) and tPA recombinant protein were both used to treat ischemic stroke. However, these treatments have dangerous complications regarding reperfusion-injury (173). Reperfusion-injury generally causes oxidative stress, calcium overload and excitatory toxicity (174). At present, edaravone, butylphenol and other drugs are often used in the clinical treatment of stroke to alleviate the brain injury caused by calcium overload and excess ROS. In addition, mitochondrial dysfunction is deemed as a marker of ischemic stroke (175). Therefore, drugs that target mitochondria and directly or indirectly affect NLRP3 inflammasome to alleviate brain injury from the aspects of ROS and calcium overload are summarized in the present review (Table I).

MCC950. As a sulfonylurea-containing compound, MCC950 was first identified as an IL-1β inhibitor (198). Then, MCC950 was also used as a specific inhibitor of NLRP3 inflammasome (199,200). The OGD/R-induced BV-2 cells and MCAO rats showed high expression of Drp1 and mitochondrial fission, as well as NLRP3 inflammasome activation, which were abolished by MCC950 treatments (191). Oxidative stress, mainly caused by mitochondria, was reported to be a crucial mechanism for brain damage following ischemic stroke. And NLRP3 inflammasome perpetuates oxidative stress. MCC950 application inhibits the effect of NLRP3 on brain oxidative stress in the animal model of transient global cerebral ischemia (201). In addition, MCC950 administration attenuated brain edema, reduced NADPH oxidase and infarct area and improved the nervous system in a MCAO rat model with reperfusion induced by hyperglycemia (202). Moreover, glibenclamide is a potent NLRP3 inflammasome inhibitor (203) that belongs to a class of medications known as sulfonylureas. Its neuroprotective role is due to its effect in reducing inflammatory response and endothelial cell death (204).

Idebenone. Idebenone was originally used as a drug to treat dementia. It was regarded as a potent antioxidant (205) which is used as a protective agent for mitochondria (206). Upon OGD/R, mtDNA and mtROS were released, resulting in accumulation of oxidized mtDNA in the cytoplasm which binds to and activates NLRP3 to initiate inflammation. Furthermore, idebenone treatment inhibited this process. NLRP3 was activated in microglia of ischemia-reperfusion rats *in vivo*. Inhibition of NLRP3 was observed in idebenone treatment which attenuated neurological deficit and reduced infarct volume (33).

Diazoxide. Diazoxide, an activator of mitochondrial K-ATP (207), prevents cytochrome c release and stabilizes mitochondrial function (208). Furthermore, diazoxide protects neurons during ischemia-reperfusion injury (209). Thus, diazoxide plays a crucial role in stabilizing mitochondrial function and in protecting neuronal survival. Indeed, mitochondrial dysfunction plays a pivotal role in the initiation and activation of the NLRP3 inflammasome (210). Diazoxide prohibits NLRP3 inflammasome activation to prevent inflammation (211). In addition, diazoxide improves mitochondrial dysfunction following ORG/R in primary microglia BV2 cell

Table I. Drugs that target mitochondria and NLRP3 inflammasome.

Drug	Mitochondrial associated protein targets	NLRP3 inflammasome targets	Model	(Refs.)
Umbelliferone	ROS/TXNIP	NLRP3/IL-1β/Caspase-1/IL-18	MCAO/R	(176)
Curcumin	ROS/TXNIP	NLRP3/IL-1β/Caspase-1	MCAO	(177)
Ruscogenin	ROS/TXNIP	NLRP3/IL-1β/Caspase-1	MCAO/R OGD/R	(178)
resveratrol	TXNIP	NLRP3/IL-1β/Caspase-1	eMCAO	(179)
tPA	TXNIP	NLRP3/IL-1β/ASC/Caspase-1	t-MCAO	(180)
Z-Guggulsterone	TXNIP	NLRP3/IL-1β/IL-18	MCAO/OGD	(181)
Malibatol A	ROS	IL-1β	MCAO	(182)
Sesamol	ROS	IL-1β	MCAO/R	(183)
Minocycline	ROS	NLRP3/IL-1β/IL-18	tMCAO/R OGD/R	(184)
Sinomenine	ROS	NLRP3/ASC/IL-1β/Caspase-1/IL-18	MCAO/OGD	(185)
Irisin	ROS	NLRP3/IL-1β/Caspase-1	OGD	(186)
apocynin	ROS	NLRP3/IL-18/IL-1β/ASC/Caspase-1	MCAO/R	(187)
Rosuvastatin	ROS	NLRP3	MCAO	(188)
arginase	ROS	IL-1β	MCAO	(189)
Medioresinol	mtROS	IL-1β/NLRP3/Caspase-1/ASC/	tMCAO	(190)
miR-668	Drp-1/ROS	NLRP3/IL-1β	tMCAO/R OGD/R	(148)
3-n-butylphthalide	Drp-1/ROS	IL-1β	OGD	(32)
Ketogenic Diet	Drp-1/ROS TXNIP/ATP	NLRP3/IL-1β/Caspase-1	MCAO/R OGD/R	(147)
Panax ginseng and *Angelica sinensis*	Drp-1	IL-1β/NLRP3/Caspase-1	MCAO/R OGD/R	(191)
FK866	Mfn2/Drp1	NLRP3/IL-1β	CA/CPR	(162)
isoflurane	mPTP/ROS	IL-1β	MCAO/OGD	(192)
Ezetimibe	Nrf2/TXNIP	NLRP3/IL-1β/Caspase-1	MCAO	(171)
melatonin	mtDNA	IL-1β	MCAO	(193)
Necrostatin-1	RIPK	NLRP3/ASC/Caspase-1/IL-1β	MCAO	(140,141)
β-caryophyllene	RIPK	IL-1β	OGD/R MCAO/R	(194)
Isosteviol Sodium	$Ca2^{+}$/mtROS	IL-1β	hypoxia	(195)
Taxifolin	$Ca2^{+}$	IL-1β	OGD	(196)
Oxysophocarpine	$Ca2^{+}$	IL-1β	OGD/R	(197)

Focal cerebral ischemia was simulated through the MCAO *in vivo* and OGD/R *in vitro*. In MCAO and OGD/R models, drugs targeting specific targets of mitochondria and NLRP3 inflammasome for the treatment of ischemic stroke are listed. NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species; TXNIP, thioredoxin interacting protein; ASC, apoptosis-associated speck-like protein containing a CARD; MCAO, middle cerebral artery occlusion; OGD/R, oxygen-glucose deprivation/reoxygenation; tMCAO, transient MCAO; mtROS mitochondrial ROS; Drp1, dynamin-related protein 1; Mfn, mitofusin; RIPK, receptor-interacting protein kinase 1.

by preventing mitochondrial depolarization and the opening of MPTP to inhibit NLRP3 inflammasome activation (212). Therefore, maintaining mitochondrial stability and reducing NLRP3 inflammasome activation could both be potential targets of diazoxide to treat ischemic stroke.

Melatonin. Melatonin, an endogenous regulator, is a metabolite of tryptophan released from the pineal gland (213). It is involved in numerous physiological and pathophysiological processes including antioxidant (214), anti-apoptotic, and anti-inflammatory effects (215). Melatonin is of neuroprotective effect, which reduces infarct volume, lowers brain edema, and increases neurological scores. In addition, melatonin preserves mitochondrial membrane potential and mitochondrial complex I activity (216), and inhibits the opening of MPTPs and the abnormal release of cytochrome c (217), which is critical in reducing ischemia-reperfusion injury. Furthermore, melatonin is a relatively nontoxic molecule, which is safe to use in clinical trials. Previously, melatonin prevented IL-1β overexpression in the MCAO rat model (218). Additionally, Wang *et al* (219) showed that melatonin inhibited cell death, loss of mPTP, the release of mitochondrial factors, pro-IL-1β processing, and activation of caspase-1 induced by OGD. Furthermore, it decreased infarct size and improved neurological scores after MCAO in mice (219,220). Consequently, melatonin exerts neuroprotective and anti-inflammatory effects by modulating multiple targets in the NLRP3 inflammation (220).

Table II. A summary of drugs in clinical trial data to treat ischemic stroke.

Drug	Trial phase	Trial length	Patients recruited	Dosage	Main results	Reference or trial identifier
Idebenone	Phase 2	28 days	Patients with the A3243G mitochondrial DNA mutation and MELAS	900 mg/day or 2,250 mg/day	High doses of idebenone can reduce venous and brain lactate concentrations and lighten fatigue	NCT00887562
Melatonin	Phase 4	14 days	Acute ischemic stroke	14 mg/daily	No results posted	NCT01863277
Minocycline	Phase 1 Phase 2	3 months	Acute ischemic stroke	Minocycline was administered intravenously within 6 h of stroke symptom onset in preset dose tiers of 3, 4.5, 6, or 10 mg/kg daily over 72 h	Minocycline may be an ideal agent to use with tissue plasminogen activator	NCT00630396
Minocycline	Phase 2 Phase 3	5 days	Acute ischemic stroke	Minocycline will be administered either intravenously or orally once daily for 5 days	No results posted	NCT03320018
3-n-butylphthalide	Phase 4	90 days	Ischemic stroke	25 mg butyphthalide and 0.9 mg/kg rtPA intravenously. Next day, butalbital 25 mg/day twice for 14 days, followed by butyphthalide capsules (0.2 g/day 3 times) orally for 90 days	No results posted	NCT03394950
3-n-butylphthalide	Phase 1 Phase 2	10 days	Acute cerebral stroke Within 12 h for the first time	Intravenous infusion of 25 mg dl-3-n-butylphthalide twice daily for 10 days	The 10-day treatment with NBP was found to be beneficial for the recovery of neurological and behavioral outcomes of patients with AIS	NCT02149875

To clarify the current progress of drugs that may target mitochondria and NLRP3 inflammasome by describing the trial phase, trial length, dosage and final main effects of relevant drugs in clinical trials. NLRP3, NLR family pyrin domain containing 3.

Anthocyanins. Anthocyanins, which are effective flavonoid antioxidants (220) are natural plant pigments with a wide range of biological activities (221,222). Anthocyanins are flavylium-based multistates (223) and can reduce the damage to neurovascular unit in MCAO rats (224). Furthermore, anthocyanins inhibit NLRP3 expression in the brains of MCAO/R rats (225) and reduce cytosolic cytochrome c release to prevent apoptosis (226). Moreover, anthocyanins are neuroprotective in mouse model of pMCAO, decrease cerebral superoxide levels and inhibit AIF release from mitochondria (227). Cui *et al* (228) showed that purified anthocyanin extracts significantly reduce the expression of caspase-1 and NLRP3 and activate Nrf2 in the ischemia-reperfusion mice brain, thereby inhibiting inflammation and protecting the brain. Thus, anthocyanins may be a potential candidate for the prevention and treatment of stroke.

6. Clinical perspectives

At present, thrombolytic therapy is the only approved treatment for acute ischemic stroke (229), but only a minority of all patients with stroke are eligible for this treatment. At present, some drugs that target mitochondria and NLRP3 inflammasome are being tested in preclinical research. Idebenone, melatonin, minocycline and 3-n-butylphthalide were examined in clinical trials (Table II). It was demonstrated that no adverse events were reported as to the clinic usage of 3-n-butylphthalide (230). 3-n-butylphthalide showed favorable results and safety in the treatment of patients with moderate acute ischemic stroke (ClinicalTrials.gov Identifier: NCT02149875). Minocycline was reported to be safe and well tolerated with half-life of ~24 h. It may be an ideal drug to treat ischemic stroke when used together with tPA (ClinicalTrials.gov Identifier: NCT00630396) (231). In addition, the North Shore University Hospital is recruiting patients to study the effect of intra-arterial neuroprotective agents (minocycline) for recanalization of ischemic stroke (ClinicalTrials.gov Identifier: NCT05032781). Furthermore, a clinical trial is comparing the efficacy and safety of low-dose rivastigmine with ezetimibe and high-dose rivastigmine in the treatment of ischemic stroke (ClinicalTrials.gov Identifier: NCT03993236). In conclusion, drugs targeting mitochondria and NLRP3 inflammasome show promising therapeutic effects.

7. Conclusion

Mitochondria are involved in various processes essential for cell survival, including energy production and physiological cell death mechanisms. Emerging knowledge about this organelle has shed light on its implication in inflammation. It is well accepted that post-ischemic neuroinflammation is one of the important mechanisms of ischemic brain injury. NLRP3 inflammasome has been found to play a key role in driving neuroinflammation in brain cells, such as cerebral microvascular endothelial cells, neurons and microglia during acute ischemic stroke. NLRP3 inflammasome was firstly activated in microglia and then expressed in microvascular endothelial cells and neurons of rat brains after ischemia-reperfusion injury. NLRP3 inflammasome can be activated by several factors, including the release of mitochondrial components, such as mtROS, cardiolipin, and mtDNA and mitochondrial related proteins, such as TXNIP and RIPK1 and some proteins that regulate the location of mitochondria. Through the present review, the close relationship between mitochondria and NLRP3 inflammasome and how mitochondrial damage contributes to ischemic damage by targeting neuroinflammation were discussed. Thus, maintaining mitochondrial homeostasis is important to ischemic stroke. Although the efficacy of tPA for acute ischemic stroke is well established, there are still serious side effects and limits. New therapeutic targets focusing on mitochondria, such as potential antioxidant or anti-inflammatory medicines, are promising therapeutic approaches in ischemic stroke. In addition, for ischemic stroke, some aforementioned drugs shall be administered in clinical trials currently recruiting patients, or are used in ongoing clinical trials or have been used in completed clinical trials. Thus, understanding the biology and regulation of inflammasome-mitochondria connections is required to treat ischemic stroke.

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Authors' contributions

XLZ designed the review, prepared the tables and figures, and wrote the manuscript. WYZ were involved in the conception and design of the study. YZ and QY searched the literature. MZ, JLG and WLZ provided helpful comments. HHL were involved in the conception and design of the study and revised the manuscript. XJJ designed the study and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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