Ageing Research Reviews 47 (2018) 67–79

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The TRPM2 channel nexus from oxidative damage to Alzheimer's pathologies: An emerging novel intervention target for age-related dementia

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ARTICLE INFO

Keywords:
Oxidative damage
Alzheimer's disease
TRPM2 channel
Neurodegeneration
Neuroinflammation
Neurovascular dysfunction

ABSTRACT

Alzheimer's disease (AD), an age-related neurodegenerative condition, is the most common cause of dementia among the elder people, but currently there is no treatment. A number of putative pathogenic events, particularly amyloid β peptide (Aβ) accumulation, are believed to be early triggers that initiate AD. However, thus far targeting Aβ generation/aggregation as the mainstay strategy of drug development has not led to effective AD-modifying therapeutics. Oxidative damage is a conspicuous feature of AD, but this remains poorly defined phenomenon and mechanistically ill understood. The TRPM2 channel has emerged as a potentially ubiquitous molecular mechanism mediating oxidative damage and thus plays a vital role in the pathogenesis and progression of diverse neurodegenerative diseases. This article will review the emerging evidence from recent studies and propose a novel 'hypothesis' that multiple TRPM2-mediated cellular and molecular mechanisms cascade Aβ and/or oxidative damage to AD pathologies. The 'hypothesis' based on these new findings discusses the prospect of considering the TRPM2 channel as a novel therapeutic target for intervening AD and age-related dementia.

1. Oxidative damage in Alzheimer's disease and dementia

It was estimated according to the World Health Organisation dementia facts published in 2017 that approximately 50 million people were living with dementia worldwide and this number is predicted to be more than tripled by 2050. Dementia has become a pressing health, social and financial matter of modern society due to the increasingly aging population and the escalating healthcare cost (The World Alzheimer Report 2015). Despite not being treated as a natural part of aging, dementia occurs when the brain is adversely affected by various conditions. Alzheimer's disease (AD) represents the most common cause of dementia and also one of the most important factors for morbidity and mortality. It is an age-related neurodegenerative disease that mainly afflicts people of 65 years and above, with the prevalence exhibiting a rapid increase with age (Nussbaum and Ellis, 2003). The brains of AD patients manifest with structural and functional loss within hippocampus, cortex and other brain regions that are responsible for learning, memory, problem-solving, language and perception, and thus AD patients suffer from progressive decline or loss of such cognitive functions that are essential for individuals to live a normal life. Currently, there is no effective treatment that can prevent AD or slow down the disease progression. It is well documented that the AD brains are presented by senile plaques with deposition of amyloid β peptides (Aβ) surrounding neurons and by neurofibrillary tangles (NFTs) formed by hyper-phosphorylated and misfolded tau proteins inside neurons. These histopathological hallmarks are invariably accompanied by widespread neuroinflammation. Aβ peptides, with $Aβ_{40}$ and $Aβ_{42}$ being the major isoforms, are generated through sequential cleavage of the amyloid precursor protein (APP), an integral membrane protein with a large extracellular N-terminus, a single membrane-spanning domain and a short cytoplasmic C-terminus, by β-secretase, which is better known as beta-site APP cleaving enzyme 1 or BACE1, and γ-secretase, a protein complex containing presenilin 1 (PS1) (Sun et al., 2015). The widely recognized amyloid cascade hypothesis posits that Aβ accumulation, resulting from elevated generation and/or reduced clearance of Aβ due to genetic and environmental factors as well as aging, is the early event that directly induces neuronal death and also initiates chronic inflammation, NFT formation and other pathological changes that are harmful to neurons (Bachurin et al., 2017; Blennow et al., 2010; Hardy and Selkoe, 2002; Selkoe and Hardy, 2016). Such a

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https://doi.org/10.1016/j.arr.2018.07.002
Received 4 May 2018; Received in revised form 5 July 2018; Accepted 9 July 2018

hypothesis for AD pathogenesis have gained strong support from preclinical and clinical studies (Selkoe and Hardy, 2016) and nonetheless evokes increasing debate, mainly because targeting Aβ generation, aggregation or clearance as a drug development strategy, despite having been intensively explored over the past decades, has thus far not led to discovery of any effective AD-modifying therapeutics (Bachurin et al., 2017; Honig et al., 2018; Kumar et al., 2018; Mullard, 2016, 2017; van Dyck, 2018). A better understanding of the complicated mechanisms underpinning AD pathogenesis and progression is urgently required, and there are also increasing interests in identifying additional or alternative intervention targets and formulating new or different therapeutic concepts (Butterfield, 2018; Butterfield and Boyd-Kimball, 2018; Corona et al., 2011; Guillot-Sestier et al., 2015; Jiang et al., 2016; Onyango, 2018; Rajendran and Paolicelli, 2018; Swerdlow et al., 2014; Weinstein, 2018; Wes et al., 2016; White et al., 2017; Wilkins et al., 2014).

Oxidative damage is a common and conspicuous feature of AD brains (Smith et al., 1996) and other neurodegenerative diseases (Jiang et al., 2016). Oxidative stress results from excessive generation of reactive oxygen species (ROS) and/or impaired ROS-scavenging mechanisms. Aβ-induced oxidative stress, which can in return enhance Aβ generation *via* stimulating the expression and activity of β- and γ-secretases (Tamagno et al., 2012), has been well recognized as one of the primary events in AD pathogenesis and progression (Bhat et al., 2015; Blennow et al., 2010; Butterfield, 2018; Butterfield and Boyd-Kimball, 2018; Hardy and Selkoe, 2002; Jiang et al., 2016; Tonnies and Trushina, 2017; Wang et al., 2014). Oxidative damage has even been proposed as a potential therapeutic target for treatment of neurodegenerative diseases, including AD (Jiang et al., 2016). However, the molecular mechanisms that sense oxidative stress/ROS and cascade to neuronal damage remain poorly defined. Transient receptor potential melastatin-related 2 (TRPM2) channel has emerged as a molecular mechanism conferring cells with the ability to sense oxidative stress/ROS and mediating oxidative damage (Hara et al., 2002; Wehage et al., 2002; Zhang et al., 2003). Consistently, a number of recent preclinical studies have accumulated strong evidence to demonstrate its crucial role in a diversity of oxidative stress-related pathological conditions, including ischemia-reperfusion brain damage (Alim et al., 2013; Gelderblom et al., 2014; Huang et al., 2017; Miyanohara et al., 2018; Nakayama et al., 2013; Shimizu et al., 2016, 2013; Ye et al., 2014), bipolar disorder (Jang et al., 2015), Parkinson's disease (PD) (Sun et al., 2018), endothelial barrier dysfunction (Hecquet et al., 2008, 2014), ischemic kidney injury (Gao et al., 2014), paracetamol overdosing-induced liver damage (Kheradpezhouh et al., 2014) and diabetes (Manna et al., 2015). This article will review the emerging evidence from recent studies and propose a novel 'hypothesis' that multiple TRPM2-mediated cellular and molecular mechanisms cascade Aβ and oxidative damage to AD-related pathologies. The 'hypothesis' based on these new findings discusses the prospect of considering the TRPM2 channel as a novel therapeutic target for intervening AD and age-related dementia.

2. A brief introduction to the TRPM2 channel

2.1. TRPM2 channel properties and activation

Mammalian cells express a family of transient receptor potential (TRP) ion channel proteins that can be divided on the basis of sequence relatedness into classical (TRPC), vanilloid (TRPV), melastatin (TRPM), ankyrin (TRPA), polycystin (TRPP) and mucolipin (TRPML) subfamilies, and these ion channels are activated by polymodal mechanisms and associated with a large and diverse number of functional roles in health and disease (Clapham, 2003; Nilius, 2007; Venkatachalam and Montell, 2007). TRPM2, as formerly known as long TRPC2, is the second member of the TRPM subfamily (Fleig and Penner, 2004; Perraud et al., 2001; Sano et al., 2001). The human TRPM2 gene is located on the chromosome 21q22.3, spans approximately 90 kb and

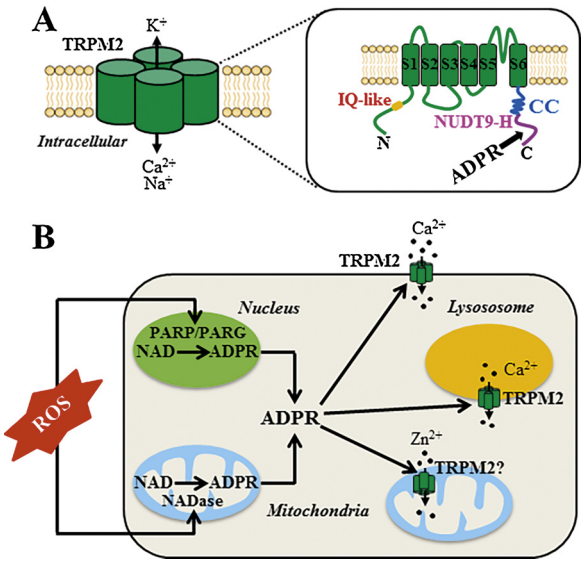

Fig. 1. The structural features, activation mechanisms and subcellular locations of the TRPM2 channel.

A, schematic illustration of the TRPM2 channel structural features. The channel is a tetramer, with each subunit composed of intracellular N- and C-termini and six transmembrane segments (S1-S6). The S5 and S6 and the re-entrance between them, from each of the four subunits, line the ion-conducting pathway in the centre of the tetrameric complex that is permeable to K^+, Na^+ and Ca^{2+}. The N-terminus contains an IQ-like motif required for calmodulin-dependent channel gating by intracellular Ca^{2+}. The C-terminus has a coiled-coil (CC) domain that mediates the tetrameric channel assembly, and the TRPM2-specific NUDT9 homology (NUDT9-H) domain that provides the binding site for the TRPM2 channel activator, ADP-ribose (ADPR). **B**, summary of the mechanisms by which the TRPM2 channel is activated by reactive oxygen species (ROS). ROS promotes ADPR generation, mainly *via* poly(ADPR) polymerase (PARP), predominantly the PARP-1, and poly(ADPR) glycohydrolase (PARG) in the nucleus and, additionally, *via* NADase in the mitochondria. The TRPM2 channel is present in the plasma membrane as a Ca^{2+}-permeable cationic channel in many cell types including neurons, microglial cells and cerebral endothelial cells. The TRPM2 channel has been shown to be located in the lysosomes as a Ca^{2+} release channel in pancreatic β-cells and dendritic cells or in the mitochondria in hippocampal neurons engaged in mitochondrial Zn^{2+} uptake.

contains 32 exons (Nagamine et al., 1998). The full-length protein (TRPM2-L) consists of 1503 amino acid residues for the human TRPM2, or 1507 amino acid residues for the rat or mouse TRPM2, with a predicted molecular weight of ~171-173 kDa (Hill et al., 2006; Nagamine et al., 1998; Uemura et al., 2005). The major structural properties of several TRP channels have been recently determined at the atomic level, including TRPC3 (Fan et al., 2018; Tang et al., 2018), TRPC4 (Vinayagam et al., 2018), TRPC6 (Tang et al., 2018), TRPV1 (Cao et al., 2013; Liao et al., 2013), TRPV2 (Huynh et al., 2016; Zubcevic et al., 2016), TRPV4 (Deng et al., 2018), TRPV5 (Hughes et al., 2018), TRPA1 (Paulsen et al., 2015), TRPM4 (Autzen et al., 2018; Duan et al., 2018; Guo et al., 2017; Winkler et al., 2017), TRPM8 (Yin et al., 2018), and TRPML3 (Hirschi et al., 2017) as well as TRPM2 (Zhang et al., 2018). These structures confirm high conservation of the overall membrane topology of these tetrameric ion channels. As illustrated in Fig. 1A, the TRPM2 channel subunit comprises six transmembrane segments (S1-S6) and intracellular N- and C-termini. Four subunits assemble the channel complex *via* the conserved coiled-coil (CC) domain in the proximal C-terminus (Fujiwara et al., 2008; Jiang, 2007; Mei et al., 2006; Tsuruda et al., 2006). The fifth and sixth transmembrane segments and the re-entrant loop between them, from each of the four subunits, form the aqueous pore in the centre of a tetrameric complex that is permeable to Ca^{2+}, Na^+ and K^+ (Fig. 1A) (Mederos y Schnitzler et al., 2008; Xia et al., 2008). The TRPM2 channel is gated by intracellular ADP-ribose (ADPR) upon binding to the TRPM2-specific NUDT9-H domain in the

distant C-terminal tail that exhibits discernible sequence homology with the ADPR-hydrolyzing enzyme NUDT9 (Fig. 1A) (Fliegert et al., 2017b; Heiner et al., 2003; Kuhn et al., 2017; Kuhn and Luckhoff, 2004; Perraud et al., 2001; Yu et al., 2017). Several ADPR analogues, including 2′-O-acetyl-ADPR, 2′-deoxy-ADPR and ADPR-2′-phosphate, are thought to be also capable of gating the TRPM2 channel (Fliegert et al., 2017a; Grubisha et al., 2006; Toth et al., 2015), whereas there is still lack of consensus whether other structurally or metabolically related compounds, such as cyclic ADPR, nicotinamide adenine dinucleotide (NAD), nicotinic acid adenine dinucleotide, and nicotinic acid adenine dinucleotide-2′-phosphate, directly bind to and activate the TRPM2 channel (Beck et al., 2006; Kolisek et al., 2005; Toth and Csanady, 2010; Toth et al., 2015). Intracellular Ca^{2+} can also open the TRPM2 channel through the IQ-like calmodulin-binding motif in the N-terminus (Fig. 1A) and thus Ca^{2+}-induced channel activation can occur independently of ADPR or in synergy with ADPR (Du et al., 2009; Tong et al., 2006). As already mentioned above, the TRPM2 channel is highly sensitive to activation by ROS, gaining its reputation as an oxidative stress sensor or mediator (Jiang et al., 2010; Knowles et al., 2013; Li et al., 2015, 2017a; Miller and Zhang, 2011; Ru and Yao, 2014; Syed Mortadza et al., 2015; Takahashi et al., 2011; Yamamoto and Shimizu, 2016). However, ROS activate the TRPM2 channel indirectly and mainly *via* promoting ADPR generation from NAD that is mediated by p(ADPR) polymerase (PARP), particularly PARP-1, and p(ADPR) glycohydrolase (PARG) in the nucleus (Fig. 1B) (Buelow et al., 2008; Fonfria et al., 2004; Hecquet et al., 2008; Jia et al., 2011; Jiang et al., 2010; Park et al., 2014). There is evidence to suggest that NADase-mediated ADPR generation from NAD in the mitochondria also contributes to ROS-induced TRPM2 channel activation (Fig. 1B) (Perraud et al., 2005).

2.2. TRPM2 channel expression and subcellular location

The TRPM2 channel exhibits wide tissue and cell distribution throughout the body and is expressed in both excitable and non-excitable cells (Belrose and Jackson, 2018; Jiang et al., 2010; Knowles et al., 2013; Li et al., 2017a; Perraud et al., 2005; Sumoza-Toledo and Penner, 2011; Syed Mortadza et al., 2015; Turlova et al., 2018). The TRPM2 channel in many cell types examined so far functions as a Ca^{2+}-permeable non-selective cation channel in the plasma membrane (Fig. 1B). Evidence also exists to suggest its localization in the membranes of intracellular organelles in some cell types (Fig. 1B), for example, in the lysosomes as a Ca^{2+} release channel in pancreatic β-cells, dendritic cells and endothelial cells (Abuarab et al., 2017; Lange et al., 2009; Manna et al., 2015; Sumoza-Toledo et al., 2011) and, as discussed below, in the mitochondria implicated in mitochondrial Zn^{2+} uptake in hippocampal neurons (Li and Jiang, 2018).

The TRPM2 channel is abundantly expressed in the brain. Its expression has been shown in hippocampal (Bai and Lipski, 2010; Belrose et al., 2012; Jia et al., 2011; Olah et al., 2009; Verma et al., 2012; Xie et al., 2011; Ye et al., 2014), cortical (Kaneko et al., 2006), striatal (Hill et al., 2006) and dopaminergic neurons (Chung et al., 2011; Sun et al., 2018), which are well known for their key role in determining learning, memory and other cognitive functions. The TRPM2 channel is also expressed in glial cells such as astrocytes (Lee et al., 2010; Wang et al., 2016), particularly microglial cells that are known as the brain-resident macrophage cells and thus are critical for immune responses (Jeong et al., 2017; Kraft et al., 2004; Miyake et al., 2014; Miyanohara et al., 2018; Syed Mortadza et al., 2017). Furthermore, TRPM2 channel expression has been documented in cerebrovascular endothelial cells (Park et al., 2014) and pericytes (Jiang et al., 2017), which have vital roles in neurovascular functions, such as regulation of cerebral blood flow (CBF) and formation of blood brain barrier (BBB). As discussed next, recent studies have shown that the Aβ/ROS-induced TRPM2 channel activation leads to synaptic loss, neuronal death, microglial activation and neuroinflammation, and neurovascular dysfunction, providing strong evidence to imply an important role for the TRPM2 channel in multiple cellular and molecular mechanisms for AD pathogenesis and progression.

3. Deletion of the TRPM2 expression halts Aβ-induced neurodegeneration and cognitive impairment in an AD mouse model

A large number of transgenic AD mice have bene generated and these mouse models, despite bearing various caveats, have been highly valuable for advancements in understanding AD pathogenesis and preclinical testing of drugs (Jankowsky and Zheng, 2017). The APP/PS1 mice, which co-express a chimeric mouse/human APP with the Swedish mutations (K670N and M671L) and human PS1 with the exon-9 deletion (Jankowsky et al., 2003) and exhibit excessive generation of Aβ and amyloid deposits in hippocampus and cortex in aged brains, are a widely-used model for studying Aβ-induced pathogenesis. A recent study has used this AD mouse strain to investigate the role of the TRPM2 channel in mediating Aβ-induced neurodegeneration, microglial activation and cognitive deficit (Ostapchenko et al., 2015). As previously documented, the APP/PS1 mice showed synaptic loss in the hippocampus as evidenced by reduced expression of synapse-specific protein synaptophysin, and microglial activation as indicated by upregulated expression of the ionised calcium binding adapter molecule 1 protein, a microglial activation marker. Furthermore, the APP/PS1 mice exhibited severely impaired age-related spatial memory as examined using the Barnes test. Genetic deletion or knockout of the TRPM2 expression (TRPM2-KO) in the wild-type (WT) C57BL/6 J mice used to generate the APP/PS1 mice resulted in no significant effect. However, TRPM2-KO in the APP/PS1 mice, while without discernible change in amyloid deposition, completely reversed synaptic loss, microglial activation, and aging-related cognitive impairment. These results provide compelling evidence to support a critical role for the TRPM2 channel in AD pathogenesis (Ostapchenko et al., 2015). However, this study has not addressed the molecular mechanisms by which Aβ peptides induce the TRPM2 channel activation to signal neurotoxicity and adverse neurological outcomes.

4. TRPM2 channel as part of a positive feedback loop for $A\beta_{42}$-induced neuronal death

4.1. Role of the TRPM2 channel in ROS/$A\beta_{42}$-induced neuronal death

An early electrophysiological study demonstrated expression of a H_2O_2-sensitive Ca^{2+}-permeable non-selective cation channel in cultured rat striatal neurons with biophysical properties characteristic of the recombinant TRPM2 channels and responsible for H_2O_2-induced Ca^{2+} influx to increase the intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) (Smith et al., 2003). A separate study showed that H_2O_2 induced Ca^{2+} responses and cell death in cultured rat striatal neurons and that such H_2O_2-induced effects were attenuated by overexpression of TRPM2-S (Fonfria et al., 2005), a short alternative splicing variant that does not form a functional channel on its own but, when co-expressed with TRPM2-L, exerts a dominant negative inhibition of the TRPM2 channel function (Zhang et al., 2003). These observations are in support of a role for the TRPM2 channel in mediating H_2O_2-induced Ca^{2+} signalling and neuronal death in striatal neurons. This study went on to enquire the role of the TRPM2 channel in striatal neuronal death induced by exposure to $A\beta_{42}$ (Fonfria et al., 2005). Exposure of cultured striatal neurons to 20 μM $A\beta_{42}$ for 2 days led to significant neuronal death, which was also mitigated by overexpression of TRPM2-S. Thus, this study, albeit using $A\beta_{42}$ at a very high concentration, provided the first indication for a role of the TRPM2 channel in mediating $A\beta_{42}$-induced neuronal death. Our recent study has examined the role of the TRPM2 channel in cultured mouse hippocampal neurons in mediating neuronal death induced by exposure to more pathologically relevant

concentrations of H_2O_2 (30–300 μM) and $A\beta_{42}$ (~0.2-1 μM) (Li and Jiang, 2018; Li et al., 2017b). Exposure to H_2O_2 or $A\beta_{42}$ induced concentration-dependent neuronal death, which was suppressed by treatment with 2-aminoethoxydiphenyl borate (2-APB) or N-(p-amylcinnamoyl)anthranilic acid (ACA), which are known to inhibit the TRPM2 channel, prior to and during exposure to H_2O_2 or $A\beta_{42}$. Moreover, H_2O_2/$A\beta_{42}$-induced hippocampal neuronal death was strongly attenuated or completely prevented by TRPM2-KO. These results provide pharmacological and genetic evidence that consistently supports a crucial role for the TRPM2 channel in mediating ROS/$A\beta_{42}$-induced neuronal death of pathological relevance (Li and Jiang, 2018; Li et al., 2017b).

4.2. Role of NOX-mediated ROS generation and PARP-1 activation in $A\beta_{42}$-induced TRPM2 channel activation and neuronal death

There is substantial evidence to indicate that ROS induces the TRPM2 channel activation and causes cell death in neuronal (Fonfria et al., 2005; Jia et al., 2011; Li et al., 2017b; Shimizu et al., 2013; Sun et al., 2018) and non-neuronal cells *via* stimulating PARP-1 (Manna et al., 2015; Mortadza et al., 2017; Zou et al., 2013). Our recent study has therefore examined the role of ROS generation and PARP-1 activation in mediating $A\beta_{42}$-induced TRPM2 channel activation and neuronal death in cultured hippocampal neurons (Li and Jiang, 2018). Exposure to $A\beta_{42}$ markedly increased ROS generation, which was largely prevented by treatment, prior to and during exposure to $A\beta_{42}$, with apocynin or diphenyleneiodonium (DPI), two generic inhibitors of nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidases (NOX), or GKT13831, a NOX1/4-selective inhibitor, and also by treatment with Gö6967, a protein kinase C (PKC) inhibitor. $A\beta_{42}$-induced neuronal death was also strongly or completely inhibited by such pharmacological interventions. These results are in good agreement with the importance of NOX expression in oxidative stress-induced neurodegeneration, particularly Aβ-induced AD pathogenesis (Nayernia et al., 2014; Zekry et al., 2003). In addition, $A\beta_{42}$-induced neuronal death was strongly suppressed by treatment with PJ34 or DPQ, two structurally different PARP-1 inhibitors, prior to and during exposure to $A\beta_{42}$ (Li and Jiang, 2018). The above-mentioned study by Fonfria et al reported a similar inhibition of $A\beta_{42}$-induced striatal neuronal death by treatment with SB-750139, another PARP-1 inhibitor (Fonfria et al., 2005). Furthermore, there is evidence to suggest that mitogen-activated protein kinase (MEK) and downstream extracellular signal-regulated kinase (ERK) signalling pathway is important in regulating oxidative stress-induced PARP-1 activation in microglial cells, oligodendrocytes and lymphocytes (Akhiani et al., 2014; Domercq et al., 2013; Kauppinen et al., 2006). Consistently, $A\beta_{42}$-induced hippocampal neuronal death was completely prohibited by treatment with U0126, a MEK/ERK inhibitor, prior to and during exposure to $A\beta_{42}$ (Li and Jiang, 2018). Taken together, these findings suggest that PKC/NOX-mediated ROS generation and subsequent activation of MEK/ERK and PARP-1 mediate $A\beta_{42}$-induced TRPM2 channel activation and neuronal death in hippocampal neurons (Fig. 2).

4.3. TRPM2-mediated alterations of intracellular Ca^{2+} and Zn^{2+} homeostasis in $A\beta_{42}$-induced neuronal death

Intracellular Ca^{2+} and Zn^{2+} are important in numerous biochemical and physiological processes but it is also well recognized that disruption in the intracellular Ca^{2+} and Zn^{2+} homeostasis is highly detrimental to cell survival, particularly for neurons (Alzheimer's Association Calcium Hypothesis, 2017; Berridge, 2010; Berridge et al., 2003; Corona et al., 2011; Ji and Weiss, 2018; LaFerla, 2002; Li et al., 2015; Overk and Masliah, 2017; Shuttleworth and Weiss, 2011; Syntichaki and Tavernarakis, 2003; Thibault et al., 2007; Zundorf and Reiser, 2011). Several recent studies have gathered evidence to suggest that the TRPM2 channel functions as a Ca^{2+}-permeable channel on the

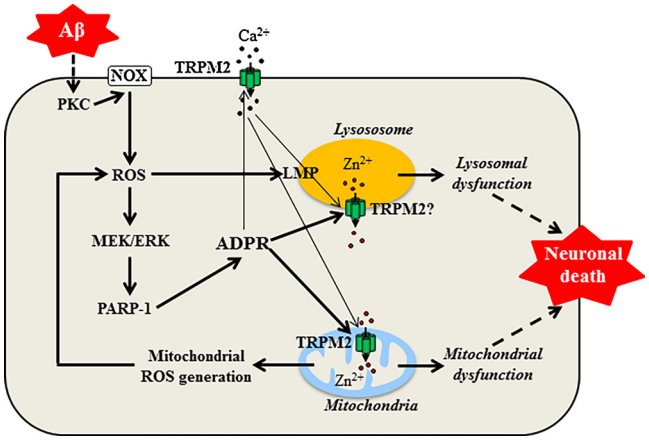

Fig. 2. The role of the TRPM2 channel in hippocampal neurons in a vicious positive feedback loop mechanism driving $A\beta_{42}$/ROS-induced neuronal death.

Summary of the positive feedback loop mechanism proposed for $A\beta_{42}$-induced TRPM2 channel activation and neuronal death in hippocampal neurons. Exposure to $A\beta_{42}$ activates protein kinase C (PKC) and NADPH-dependent oxidases (NOX), leading to ROS generation. ROS activates mitogen-activated protein kinase (MEK) and downstream extracellular signal-regulated kinase (ERK) to stimulate poly(ADPR) polymerase-1 (PARP-1) in the nucleus for ADPR generation. ADPR opens the TRPM2 channel on the cell surface that mediates extracellular Ca^{2+} influx. ROS may also induce lysosomal membrane permeation (LMP), resulting in lysosomal dysfunction and lysosomal Zn^{2+} release to the cytosol. ADPR, in synergy with Ca^{2+}, opens the TRPM2 channel located in the mitochondria (presumably in the inner membrane), resulting in mitochondrial Zn^{2+} accumulation. Mitochondrial Zn^{2+} accumulation triggers mitochondrial dysfunction, cytochrome-c release and ROS generation. Mitochondrial ROS generation further elevates the ROS levels and thereby forms a vicious positive feedback to cause lysosomal and mitochondrial dysfunctions and ultimately drive neurons to die.

cell surface and mediates ROS-induced extracellular Ca^{2+} influx to raise the $[Ca^{2+}]_i$ in striatal, cortical, hippocampal and dopaminergic neurons (Fonfria et al., 2005; Kaneko et al., 2006; Li et al., 2017b; Sun et al., 2018). Such TRPM2-mediated Ca^{2+} signalling in cortical neurons has been proposed to be important in mediating ROS-induced neuronal death (Kaneko et al., 2006). In striatal neurons, exposure to 20 μM $A\beta_{42}$ induced a detectable increase in the $[Ca^{2+}]_i$. Such Ca^{2+} response was antagonized by treatment with SB-750139 or by overexpression of TRPM2-S (Fonfria et al., 2005), supporting a role for the TRPM2 channel in $A\beta_{42}$-induced Ca^{2+} signalling. However, it is yet unclear how critical such TRPM2-mediated Ca^{2+} signalling is in $A\beta_{42}$-induced neuronal death. As shown in our previous study, TRPM2 channel activation is required for a salient rise in the intracellular Zn^{2+} concentration ($[Zn^{2+}]_i$) in hippocampal neurons during reperfusion following transient ischemia *in vivo* and *in vitro* and such alterations in the intracellular Zn^{2+} homeostasis are strongly correlated with neuronal death (Ye et al., 2014). In addition, direct exposure of cultured hippocampal neurons to H_2O_2 can lead to an increase in the $[Zn^{2+}]_i$ that is strongly dependent of extracellular Ca^{2+} (Li et al., 2017b; Ye et al., 2014), which is consistent with the importance of the Zn^{2+} and Ca^{2+} synergism in inducing neuronal death (Ji and Weiss, 2018). Our recent study shows that exposure to $A\beta_{42}$ up to 1 μM elevated the $[Zn^{2+}]_i$ but failed to evoke any measureable increase in the $[Ca^{2+}]_i$ in hippocampal neurons (Li and Jiang, 2018). Both H_2O_2/$A\beta_{42}$-induced increase in the $[Zn^{2+}]_i$ and neuronal death were completely prevented by treatment with PJ34 or 2-APB, and by TRPM2-KO as well as by treatment with TPEN used as a Zn^{2+}-specific chelator (Li and Jiang, 2018; Li et al., 2017b; Ye et al., 2014). It is worth pointing out here that whether the TRPM2 channel is permeable to Zn^{2+} still remains a matter of further investigation (Li and Jiang, 2018; Li et al., 2017b). Regardless, all the evidence from pharmacological and genetic interventions points to a

crucial role that the TRPM2 channel plays in mediating ROS/$A\beta_{42}$-induced alterations in the intracellular homeostasis of Ca^{2+} and particularly Zn^{2+}, that lead to neuronal death.

Single cell imaging studies in conjunction with using intracellular organelle specific markers have revealed a low level of intracellular Zn^{2+} in untreated hippocampal neurons that exist in discrete puncta being mainly located within the lysosomes but not mitochondria or endoplasmic reticulum (Li and Jiang, 2018; Li et al., 2017b; Ye et al., 2014). Exposure to H_2O_2 or $A\beta_{42}$ induced an increase in the $[Zn^{2+}]_i$ that was accompanied by loss of lysosomal Zn^{2+} and, additionally, loss of LysoTracker staining that indicates lysosomal dysfunction. Exposure to $A\beta_{42}$ also resulted in a significant reduction in acridine orange staining in hippocampal neurons, further supporting $A\beta_{42}$-induced lysosomal dysfunction. A previous study showed that H_2O_2 promoted lysosomal membrane permeation (LMP) in hippocampal neurons leading to neuronal death (Hwang et al., 2008). It is tempting to speculate, although supporting evidence still awaits, that such a mechanism is responsible for $A\beta_{42}$-induced lysosomal dysfunction and contributes to $A\beta_{42}$-induced hippocampal neuronal death (Fig. 2). $A\beta_{42}$-induced lysosomal dysfunction and increase in the $[Zn^{2+}]_i$ were curtailed by treatment with TPEN, PJ34 or 2-APB, and also by TRPM2-KO (Li and Jiang, 2018). Interestingly, exposure to bafilomycin, which is known to induce lysosomal dysfunction, increased the $[Zn^{2+}]_i$ in hippocampal neurons, like exposure to H_2O_2 or $A\beta_{42}$. Collectively, these observations are consistent with the idea that lysosomal dysfunction acts as a mechanism for $A\beta_{42}$-induced lysosomal Zn^{2+} release to increase the $[Zn^{2+}]_i$. As introduced above, the TRPM2 channel has been described to be located in the lysosomes, where it functions as a Ca^{2+} release channel in pancreatic β-cells, dendritic cells and endothelial cells (Abuarab et al., 2017; Lange et al., 2009; Manna et al., 2015; Sumoza-Toledo et al., 2011). Moreover, recent studies provide evidence to suggest that the lysosome-residing TRPM2 channel is critical for H_2O_2-induced lysosomal Zn^{2+} release and cell death in pancreatic β-cells and endothelial cells (Abuarab et al., 2017; Manna et al., 2015). Further efforts are needed to clarify whether the TRPM2 channel is present in the lysosomes in hippocampal neurons and, if it is true, whether it has a role in mediating ROS/$A\beta_{42}$-induced lysosomal Zn^{2+} release and neuronal death.

Single cell imaging studies have also shown that exposure to H_2O_2 or $A\beta_{42}$ disrupted mitochondrial Zn^{2+} homeostasis and impaired mitochondrial functions in cultured hippocampal neurons (Li and Jiang, 2018; Li et al., 2017b). Exposure to H_2O_2 or $A\beta_{42}$ increased the Zn^{2+} level in the mitochondria, which was abolished by treatment with TPEN, PJ34 or 2-APB, and by TRPM2-KO. Bafilomycin-induced lysosomal dysfunction also led to mitochondrial Zn^{2+} accumulation. These results together support the notion that mitochondrial Zn^{2+} accumulation occurs as a sequela of lysosomal dysfunction and lysosomal Zn^{2+} release (Li and Jiang, 2018; Li et al., 2017b). Surprisingly, bafilomycin-induced mitochondrial Zn^{2+} accumulation was also prevented by treatment with PJ34 or 2-APB, and by TRPM2-KO, indicating strong dependence of the TRPM2 channel. Such observations raised an intriguing question with respect to the expression and function of the TRPM2 channel in the mitochondria. Both confocal imaging of the subcellular location of the TRPM2 immunoreactivity in cultured hippocampal neurons and western blotting analysis of proteins in isolated mitochondria consistently suggest mitochondrial location of the TRPM2 channel (Li and Jiang, 2018). In further support of this notion, treatment with ADPR, the TRPM2 channel specific activator, induced substantial Zn^{2+} accumulation in individual mitochondria isolated from WT but not TRPM2-KO hippocampal neurons. In addition, ADPR-induced mitochondrial Zn^{2+} accumulation was only observed in the presence but not in the absence of Ca^{2+}, consistent with Ca^{2+} being critical for ADPR-induced TRPM2 channel activation in hippocampal neurons (Olah et al., 2009; Ostapchenko et al., 2015; Ye et al., 2014). Mitochondrial location of the TRPM2 channel and requirement for ADPR-induced mitochondrial Zn^{2+} accumulation were nicely recapitulated in HEK293 cells by introducing heterologous expression of the human TRPM2 channel (Li and Jiang, 2018). Taken together, these results have led to the proposal that the TRPM2 channel is located in the mitochondria and plays an important role in determining mitochondrial Zn^{2+} accumulation. However, further efforts are required to elucidate whether the TRPM2 channel itself or distinct TRPM2-dependent molecular mechanisms mediate mitochondrial Zn^{2+} accumulation. The TRPC3 channel, a member of the TRPC subfamily, has been reported to be located in the mitochondria and regulate mitochondrial Ca^{2+} homeostasis (Feng et al., 2013). It is also interesting to investigate whether the TRPM2 channel participates in mitochondrial Ca^{2+} homeostasis as well as mitochondrial Zn^{2+} homeostasis, as both are known to be critical in determining the neuronal mitochondrial function (Ji and Weiss, 2018).

Studies examining the brains of AD patients and AD mouse models have gathered a large body of evidence that supports a role for mitochondrial dysfunction and associated oxidative stress in AD-related pathologies (Fukui and Moraes, 2008; Kerr et al., 2017; Maruszak and Zekanowski, 2011; Mattson et al., 2008; McManus et al., 2011; Onyango, 2018; Swerdlow et al., 2014; Wang et al., 2014). Our recent studies further considered the role of the TRPM2 channel, particularly TRPM2-dependent mitochondrial Zn^{2+} accumulation, in H_2O_2/$A\beta_{42}$-induced mitochondrial dysfunction and mitochondrial ROS generation in hippocampal neurons (Li and Jiang, 2018; Li et al., 2017b). A previous study reported mitochondrial fragmentation, mitochondrial impairment and oxidative stress in neurons in the close vicinity of amyloid plaques (Xie et al., 2013) in the APP/PS1 mice, which co-express the chimeric mouse/human APP with the Swedish mutations and human PS1 carrying the A246E mutation (Borchelt et al., 1997). In consistency with such *in vivo* observations, our recent studies show that exposure to H_2O_2 or $A\beta_{42}$ induced tabular-to-fragmented change in the mitochondrial morphology, release of cytochrome-c, and mitochondrial ROS generation (Li and Jiang, 2018; Li et al., 2017b). Interestingly, H_2O_2/$A\beta_{42}$-induced morphological change of the mitochondria and mitochondrial ROS generation were abolished by treatment with TPEN, PJ34 or 2-APB, and by TRPM2-KO (Li and Jiang, 2018; Li et al., 2017b). In addition, bafilomycin-induced lysosomal dysfunction potently stimulated mitochondrial ROS generation, which was also blocked by treatment with PJ34 or 2-APB, and by TRPM2-KO (Li and Jiang, 2018). These observations have led us to suggest that TRPM2-dependent mitochondrial Zn^{2+} accumulation initiates ROS/$A\beta_{42}$-induced mitochondrial dysfunction and neuronal death (Fig. 2).

PKC/NOX-mediated ROS generation, as discussed above, is crucial in $A\beta_{42}$-induced hippocampal neuronal death. Interestingly, inhibition of PKC or NOX also strongly suppressed $A\beta_{42}$-induced lysosomal dysfunction and lysosomal Zn^{2+} release and, furthermore, mitochondrial Zn^{2+} accumulation and mitochondrial dysfunction (Li and Jiang, 2018). These results suggest that $A\beta_{42}$-induced PKC/NOX-mediated ROS generation acts as a mechanism that initiates lysosomal dysfunction and lysosomal Zn^{2+} release and subsequent TRPM2-dependent mitochondrial Zn^{2+} accumulation and mitochondrial dysfunction. In particular, these findings have led us to hypothesize, as summarized in Fig. 2, that mitochondrial ROS generation closes in a vicious positive feedback loop to sustain or build up oxidative stress and ultimately drive neuronal death without the need of further or continuous exposure to ROS or $A\beta_{42}$ (Li and Jiang, 2018). Such a mechanism, while still remaining hypothetic and needing further investigations, offers some explanation for the poor outcomes of anti-Aβ therapeutics alone treating AD at the later stage.

5. TRPM2 channel in $A\beta_{42}$-induced microglial cell activation and neuroinflammation

5.1. Microglial cell activation in AD-related neuroinflammation

Microglial cells, the major cell population in the brain, are

functionally similar to macrophage cells in the systemic immune system, and work together with other glial cells and the cerebrovascular unit to uphold an optimal environment for neurons in the brain to function. In the healthy brain, microglial cells assume a ramified morphology defined by small cell body with elongated and branched processes. These cells unceasingly scrutinize the brain parenchyma and eliminate cellular debris (Colonna and Butovsky, 2017; Hong and Stevens, 2016; Wolf et al., 2017). Microglial cells are readily activated by damage-associated molecular patterns (DAMP) molecules released by host cells such as Aβ or pathogen-associated molecular patterns (PAMP) molecules from infection with lipopolysaccharide (LPS) being one such example. Upon activation, microglial cells adopt distinct morphologies characterized by enlarged cell body and retracted processes. Activated microglial cells can initiate potent inflammatory responses by generating a number of pro-inflammatory mediators, including ROS and cytokines, to restore the brain homeostasis. It should be pointed out, microglial cells have a protective role in AD by clearing Aβ, but such a beneficial capacity deteriorates and eventually becomes inefficient with aging or upon exposure to excessive Aβ. However, there is a large volume of evidence from studies examining the brains of AD patients and rodent AD models to support that chronic or dysregulated activation of microglial cells and alterations in their activation states, in concerted actions with DAMP molecules released by degenerating neurons, can create a vicious positive feedback that results in generation of excessive proinflammatory mediators to damage synapses and neurons, a process collectively termed neuroinflammation, and thus restoration of the normal functional states of microglia has been proposed as a therapeutic approach to AD (Block et al., 2007; Colonna and Butovsky, 2017; Glass et al., 2010; Heneka et al., 2015, 2014; Heppner et al., 2015; Minter et al., 2016; Mosher and Wyss-Coray, 2014; Perry and Holmes, 2014; Prokop et al., 2013; Ransohoff, 2016; Spangenberg and Green, 2017; von Bernhardi et al., 2010; Wes et al., 2016; Wolf et al., 2017). Aβ-induced neuroinflammation *via* generation by microglial cells of excessive neurotoxic cytokines such as interleukin (IL)-1β, tumour necrosis factor (TNF)-α and IL6 plays an important role in AD pathogenesis and progression (Alam et al., 2016; Block et al., 2007; Colonna and Butovsky, 2017; Heneka et al., 2015; Heppner et al., 2015; Hong et al., 2016; Liu and Hong, 2003; Minter et al., 2016; Spangenberg and Green, 2017; White et al., 2017; Wyss-Coray and Rogers, 2012). As already discussed above, a recent study using the APP/PS1 mice has shown that TRPM2-KO prevented Aβ-induced microglial cell activation *in vivo* (Ostapchenko et al., 2015). Consistently with such an *in vivo* study, studies from us and other researchers using cultured microglial cells provide evidence to support an important role of the TRPM2 channel in $A\beta_{42}$-induced microglial cell activation and, additionally, generation of IL-1β and TNF-α (Syed Mortadza et al., 2018; Aminzadeh et al., 2018). Moreover, these *in vitro* studies have gained further insights into the molecular or signalling mechanisms underlying $A\beta_{42}$-induced TRPM2 channel activation.

5.2. Role of the TRPM2 channel in coupling $A\beta_{42}$-induced ROS generation to NLRP3 inflammasome activation and IL-1β generation

IL-1β is a master pro-inflammatory cytokine with a key role in innate immunity (Heneka et al., 2014). IL-1β generation commonly requires two signals named priming and activation signals (Fig. 3A). LPS, derived from Gram-negative bacteria and often acting as a priming signal, interacts with the Toll-like receptor 4 (TLR4) and thereby activates its downstream signalling pathway that leads to synthesis of pro-IL-1β, the biologically inactive precursor protein. $A\beta_{42}$ is a well-recognized activation signal that promotes assembly and activation of the multi-protein complex NLRP3 inflammasome in the cytosol, composed of the nucleotide binding domain-containing leucine-rich repeat protein 3 (NLRP3), adapter protein apoptosis-associated speck-like protein, and procaspase-1. The NLRP3 inflammasome serves a platform for recruitment of pre-caspase-1 and activation of caspase-1 by cleavage and subsequently caspase-1 converts pro-IL-1β into IL-1β. A recent study has shown that genetic interruption of the NLRP3 inflammasome activation in the APP/PS1 mice, which co-express the chimeric mouse/human APP with the Swedish mutations and human PS1 with exon-9 deletion (Jankowsky et al., 2003), reduced the ability of microglial cells to generate IL-1β and enhanced Aβ clearance (Heneka et al., 2013). These results support a role for Aβ-induced NLRP3 inflammasome activation and IL-1β generation by activated microglial cells in AD pathogenesis and progression (Heneka et al., 2013, 2014), leading to the growing interest in the NLRP3 inflammasome as a therapeutic target for treatment of AD (White et al., 2017). It is well-known that a great number of DAMP/PAMP molecules, despite the striking difference in their structures, can activate the NLRP3 inflammasome in immune cells including microglial cells by stimulating ROS generation, particularly mitochondrial ROS generation, and inducing extracellular Ca^{2+} influx (Gong et al., 2018; Hafner-Bratkovic and Pelegrin, 2018; Song et al., 2017; Tschopp and Schroder, 2010). A recent study has examined the role of the TRPM2 channel in IL-1β generation by LPS-primed macrophage cells after exposure to silica, alum or charged lipids. IL-1β generation induced by these particulate crystals was impaired by TRPM2-KO or upon removal of extracellular Ca^{2+} influx, demonstrating a critical role for the TRPM2 channel or more specifically TRPM2-mediated Ca^{2+} influx in coupling mitochondrial ROS generation to NLRP3 inflammasome activation and IL-1β generation (Zhong et al., 2013). A more recent study has revealed a similar role for the TRPM2 channel in mediating $A\beta_{42}$-induced NLRP3 inflammasome activation and IL-1β maturation in LPS-primed microglial cells (Aminzadeh et al., 2018). This study shows that exposure to 10 μM $A\beta_{42}$ induced mitochondrial ROS generation and IL-1β generation, both of which were strongly inhibited or completely abolished by pre-treatment with a high concentration of DPI (20 μM) as a mitochondrial ROS inhibitor. $A\beta_{42}$-induced IL-1β generation was also reduced by pre-treatment with VAS2870 or (2R, 4R)-4-aminopyrrolidine-2,4-dicarboxylate (APDC), NOX inhibitors, N-acetylcysteine (NAC), a ROS scavenger, or DPQ. $A\beta_{42}$ induced a significant increase in the $[Ca^{2+}]_i$, which was markedly suppressed by treatment with DPI, VAS2870, or DPQ. Furthermore, $A\beta_{42}$-induced increase in the $[Ca^{2+}]_i$ was observed only in the Ca^{2+}-containing but not Ca^{2+}-free solutions and was also reduced by treatment with BAPTA-AM, a membrane-permeable Ca^{2+} chelator, to buffer the increase in the $[Ca^{2+}]_i$. Finally, $A\beta_{42}$-induced caspase-1 activation, examined by western blotting, was inhibited by treatment with DPQ or BAPTA-AM. Overall, the study provides pharmacological evidence to suggest, as summarized in Fig. 3A, that the TRPM2 channel, particularly TRPM2-mediated Ca^{2+} influx, is critical in $A\beta_{42}$-induced IL-1β generation by coupling mitochondrial and NOX-mediated ROS generation to activation of the NLRP3 inflammasome and caspase-1.

5.3. TRPM2 channel is essential for $A\beta_{42}$-induced microglial cell activation and TNF-α generation

TNF-α represents another proinflammatory cytokines that plays an important role in Aβ-induced AD-related pathologies *via* multiple and distinctive cellular and molecular mechanisms. It can induce neuronal death directly *via* activation of the TNF death receptor and also indirectly through microglial cell activation and generation of neurotoxic proinflammatory mediators (Alam et al., 2016; Block et al., 2007; Doll et al., 2015; Kalliolias and Ivashkiv, 2016). Thus, chronic neuron-specific expression of TNF-α enhanced local inflammation and neuronal death in the triple-transgenic AD (3xTg-AD) mice (Janelsins et al., 2008), which co-express human APP with the Swedish mutations and human tau with P30IL mutation together with PS1 with M146 V mutation (Oddo et al., 2003), whereas deletion of the TNF-α expression attenuated Aβ generation, amyloid deposition and microglial activation in 5XFAD AD mice (Paouri et al., 2017), in which co-expression of human APP with the Swedish (K670 N/M671 L), Florida (I716 V) and London (V717I) mutations and human PS1 with M146 L and L286 V

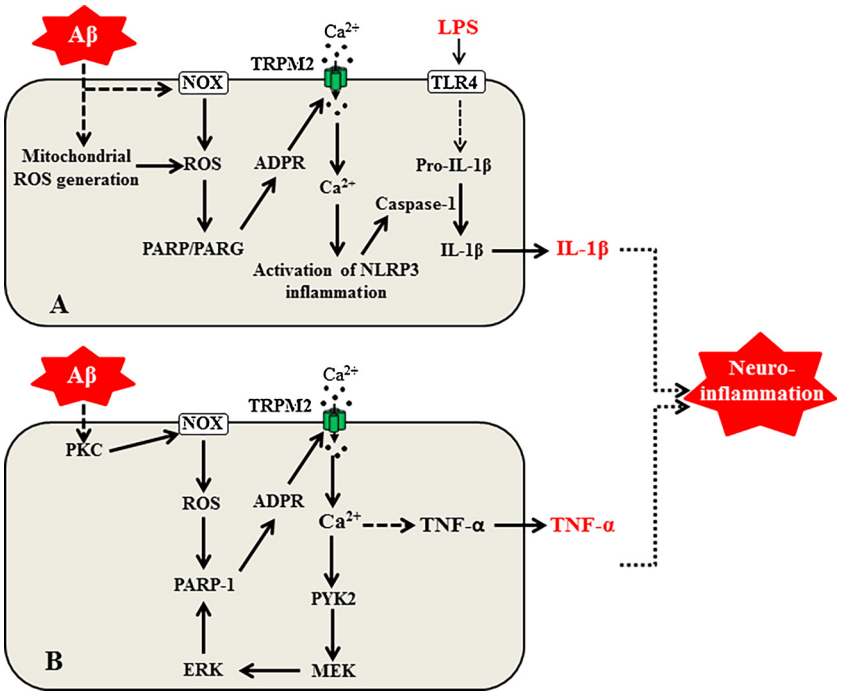

Fig. 3. The role of the TRPM2 channel in microglial cells in $A\beta_{42}$-induced mechanisms for microglial cell activation and generation of proinflammatory IL-1β and TNF-α.
A, summary of the molecular/signalling mechanisms proposed for $A\beta_{42}$-induced TRPM2 channel activation and generation of interleukin (IL)-1β by microglial cells primed with lipopolysaccharide (LPS). LPS promotes synthesis of pro-IL-1β *via* activation of the Toll-like receptor 4 (TLR4). $A\beta_{42}$ stimulates mitochondrial and NADPH-dependent (NOX)-mediated ROS generation, which in turn activates poly(ADPR) polymerase (PARP) and poly(ADPR) glycohydrolase (PARG) for ADPR generation. Activation by ADPR of the TRPM2 channel on the cell surface results in extracellular Ca^{2+} influx and an increase in the intracellular Ca^{2+} concentration that triggers activation of the NLRP3 inflammasome and caspase-1. Caspase-1 converts pro-IL-1β to IL-1β. **B**, summary of the molecular/signalling mechanisms for $A\beta_{42}$-induced TRPM2 channel activation and generation of tumour necrosis factor (TNF)-α by microglial cells. $A\beta_{42}$ induces NOX-mediated ROS generation. ROS in turn activate the TRPM2 channel on the cell surface *via* stimulating PARP-1 mediated ADPR generation in the nucleus. TRPM2 channel activation results in extracellular Ca^{2+} influx and an increase in the intracellular Ca^{2+} concentration, which triggers the expression and secretion of TNF-α. TRPM2-dependent Ca^{2+} influx activates the Ca^{2+}-sensitive tyrosine kinase PYK2 and downstream mitogen-activated kinase (MEK) and extracellular signal-regulated kinase (ERK) to further stimulate PARP-1. Such signalling pathway acts as a positive feedback mechanism for TRPM2 channel activation and TNF-α generation. Microglial generation of IL-1β and TNF-α is critical in contributing to Aβ-induced neuroinflammation.

mutations results in almost exclusive generation of $A\beta_{42}$, amyloid deposition and memory impairment (Oakley et al., 2006). Consistently, genetic ablation of the TNF type 1 death receptor (TNFR1) expression suppressed Aβ generation and cognitive dysfunction in the APP23 AD mice (He et al., 2007), in which expression of human APP with the Swedish mutations results in senile plaque formation in the cerebral cortex and hippocampus and neuronal loss in CA1 of the hippocampus (Sturchler-Pierrat et al., 1997). These findings support a significant role for TNF-α and its receptor TNFR1 in Aβ-related pathogenesis, leading to the proposal of inhibiting TNF-α generation as a therapeutic strategy treating AD. Our recent study has examined the role of the TRPM2 channel in mediating $A\beta_{42}$-induced microglial cell activation and TNF-α generation in cultured microglial cells (Syed Mortadza et al., 2018). Exposure to $A\beta_{42}$ at 30–300 nM induced concentration-dependent change in the microglial cell morphology, and an increase in the expression and secretion of TNF-α, as shown by immunocytochemistry and enzyme-linked immunosorbent assay, respectively. $A\beta_{42}$-induced changes in the cell morphology and TNF-α generation were prevented by pre-treatment with 2-APB and also by TRPM2-KO, highlighting a key role of the TRPM2 channel in mediating $A\beta_{42}$-induced microglial cell activation and TNF-α generation. $A\beta_{42}$-induced increase in the $[Ca^{2+}]_i$ was prevented by pre-treatment with 2-APB or by TRPM2-KO, and only observed in the extracellular Ca^{2+}-containing but not Ca^{2+}-free solutions (Syed Mortadza et al., 2018), demonstrating a major role for the TRPM2 channel in $A\beta_{42}$-induced Ca^{2+} signalling (Fig. 3B). This is consistent with a previous study showing cell surface expression of the TRPM2 channel in microglial cells and its critical role in mediating Ca^{2+} influx (Kraft et al., 2004). We have further demonstrated that exposure to $A\beta_{42}$ induced massive ROS generation and nuclear PARP-1 activation. $A\beta_{42}$-induced ROS generation and PARP-1 activation were strongly suppressed by pre-treatment with DPI, GKT137831 or Phox-I2, a NOX2-specific inhibitor, and also by pre-treatment with chelerythrine chloride (CTC), a PKC inhibitor. $A\beta_{42}$-induced increase in the $[Ca^{2+}]_i$ was also strongly inhibited by such pharmacological treatments as well as treatment with PJ34 or DPQ. Taken together, these results indicate that PKC/NOX-mediated ROS generation and subsequent PARP-1 activation are critical for $A\beta_{42}$-induced TRPM2 channel activation in microglial cells that leads to extracellular Ca^{2+} influx and an increase in the $[Ca^{2+}]_i$ (Fig. 3B). A previous study showed that TRPM2-mediated Ca^{2+} influx in monocytes activated PYK2, a Ca^{2+}-sensitive tyrosine kinase, and its downstream mitogen-activated kinases MEK/ERK in response to H_2O_2 (Yamamoto et al., 2008). Similarly, $A\beta_{42}$-induced increase in the $[Ca^{2+}]_i$ and PARP-1 activation in microglial cells were prevented by pre-treatment with PF431396, a PYK2 inhibitor, or U0126, a MEK/ERK inhibitor (Syed Mortadza et al., 2018). Of notice, $A\beta_{42}$-induced PARP-1 activation was significantly reduced but not completely abolished by TRPM2-KO. The $A\beta_{42}$-induced PARP-1 activity in TRPM2-KO microglial cells was eliminated by pre-treatment with DPI, GKT137831, Phox-I2 or CTC, but was not altered by pre-treatment with PF431396 or U0126 (Syed Mortadza et al., 2018). These discriminating results suggest that $A\beta_{42}$-induced PKC/NOX-mediated ROS generation and PARP-1 activation act as the mechanism initiating TRPM2 channel activation, and subsequent TRPM2 channel-mediated Ca^{2+} influx and activation of the PYK2/MEK/ERK signalling pathway provide a positive feedback mechanism to maintain the TRPM2 channel activation (Fig. 3A). $A\beta_{42}$-induced microglial cell activation and TNF-α generation were effectively prevented by treatment with PF431396 or U0126, supporting the importance of such PYK2/MEK/ERK signalling pathway-mediated positive feedback mechanism in mediating $A\beta_{42}$-induced microglial cell activation and TNF-α generation.

Collectively, these recent *in vitro* and *in vivo* studies, as illustrated in Fig. 3, provide compelling evidence that consistently supports the TRPM2 channel as a previously unrecognized mechanism mediating $A\beta_{42}$-induced generation of proinflammatory cytokines and AD-related neuroinflammation (Wei et al., 2018).

6. TRPM2 channel in cerebral endothelial cells for Aβ-induced neurovascular dysfunction

Cerebral endothelial cells form part of the neurovascular unit by lining the inner blood vessel wall and thus play a vital role in regulating CBF and maintaining BBB function (Iadecola, 2017). While ROS-induced cerebrovascular endothelial dysfunction is a well-known risk factor that enhances the susceptibility to brain pathologies such as

atherosclerosis and stroke, there is growing evidence to support a role of Aβ-induced ROS generation and subsequent impairment in cerebrovascular endothelial function in predisposing to AD (Iadecola, 2013, 2017; Koizumi et al., 2016; McDade et al., 2014; Purnell et al., 2009; Sweeney et al., 2018; Toledo et al., 2013; Zlokovic, 2011). It has been well established that the TRPM2 channel function as a cell surface Ca^{2+}-permeable channel in pulmonary artery and microvascular endothelial cells that mediates ROS-induced Ca^{2+} influx to increase in the $[Ca^{2+}]_i$ and endothelial cell death and barrier dysfunction (Hecquet et al., 2008, 2014; Mittal et al., 2018). A recent study has examined the TRPM2 channel expression in cerebrovascular endothelial cells and its role in Aβ-induced neurovascular dysfunction (Park et al., 2014). In the CD31-positive immortalized mouse brain endothelial bEEND.3 cells, intracellular application of $Aβ_{40}$ as well as ADPR elicited sizable ionic currents with a linear current-voltage relationship curve, and such currents were sensitive to blockage by 2-APB or ACA, and prevented by siRNA-mediated knockdown of the TRPM2 expression, indicating functional expression of the TRPM2 channel and its activation by $Aβ_{40}$. $Aβ_{40}$/ADPR-induced currents were also inhibited by pre-treatment with PJ34, ADP-HPD, a PARG inhibitor, tetrakis(4-benzoic acid)porphyrin chloride Mn(III) (MnTBAP), a ROS scavenger, gp91ds-tat, a NOX peptide inhibitor, or L-N^G-nitroarginine (L-NNA), a nitric oxide (NO) synthase (NOS) inhibitor. Exposure to $Aβ_{40}$ induced PARP-1 activation, which was prevented by pre-treatment with MnTBAP, tempol, another ROS scavenger, gp91ds-tat, L-NNA, or 5,10,15,20-tetrakis(4-sulfonatophenyl)porphyrinato iron(III) chloride (FeTPPS), a peroxynitrite decomposition catalyst. Overall, these results support that $Aβ_{40}$-induced NOX-mediated ROS generation and constitutive NOS-mediated NO generation, leading to peroxynitrite formation and subsequent activation of the PARP-1/PARG and TRPM2 channel in brain endothelial cells (Fig. 4). In addition, exposure to $Aβ_{40}$ induced an increase in the $[Ca^{2+}]_i$ and such Ca^{2+} responses were essentially inhibited by treatment with 2-APB, ACA or TRPM2-specific siRNA, indicating a critical role for the TRPM2 channel in $Aβ_{40}$-induced Ca^{2+} signalling *via* mediating Ca^{2+} influx, as described above in microglial cells (Fig. 3). This study performed further experiments to examine the role of the TRPM2 channel in Aβ-induced neurovascular dysfunction *in vivo* (Park et al., 2014) using the Tg2576 AD mice expressing human APP carrying with the Swedish mutations (Hsiao et al., 1996). In the WT mice, neocortical superfusion of 5 μM $Aβ_{40}$ significantly reduced the resting CBF and also attenuated the increase in CBF induced by neural activity *via* whisker stimulation or vasodilation *via* application of acetylcholine, an endothelial-dependent vasodilator. $Aβ_{40}$-induced reduction in the resting CBF and the evoked increases in CBF were prevented by neocortical application of FeTPPS, uric acid, another peroxynitrite scavenger, PJ34, or ADP-HPD, and by genetic deletion of the PARP-1 expression. Furthermore, such $Aβ_{40}$-induced changes in CBF under the resting and stimulated conditions were also effectively prevented by neocortical application of 2-APB or ACA, and by TRPM2-KO. In the Tg2576 AD mice, the evoked increases in CBF were significantly smaller compared those observed in the WT mice. Such neurovascular dysfunction in the Tg2576AD mice was fully restored by treatment with PJ34, ADP-HPD, 2-APB or ACA. Taken together, these results consistently support that the TRPM2 channel is important in linking Aβ-induced ROS generation to cerebrovascular dysfunction (Fig. 4), therefore revealing a distinct cellular mechanism by which the TRPM2 channel is engaged in Aβ-induced pathogenesis and progression (Koizumi et al., 2016; Park et al., 2014).

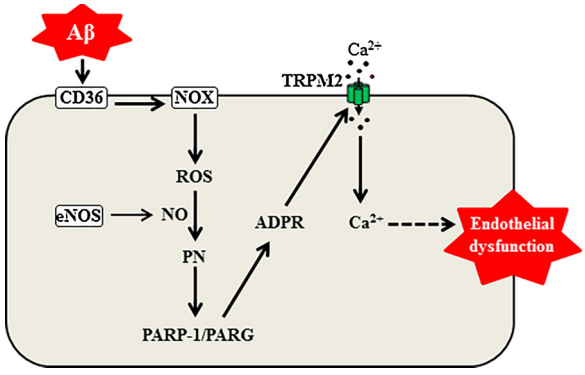

Fig. 4. The role of the TRPM2 channel in cerebral endothelial cells in Aβ-induced endothelial dysfunction.
Summary of the molecular/signalling mechanism responsible for $Aβ_{40}$-induced TRPM2 channel activation in cerebral endothelial cells and endothelial dysfunction. $Aβ_{40}$ *via* CD36 induces NADPH-dependent oxidase (NOX) activation and ROS generation. Reaction of ROS with nitric oxide (NO) constitutively generated by endothelial NO synthase (eNOS), leads to peroxynitrite formation that stimulates poly(ADPR) polymerase-1 (PARP-1) and poly(ADPR) glycohydrolase (PARG) in the nucleus to generate ADPR. ADPR opens the TRPM2 channel, resulting in extracellular Ca^{2+} influx and an increase in the intracellular Ca^{2+} concentrations that triggers endothelial and neurovascular dysfunction.

7. Closing remarks and perspective

As the world population is continually aging, the number of the elder people suffering from dementia will rise at an accelerated pace, imposing immense social and financial burdens on individuals and related families as well as severe pressure on the national healthcare service. Development of effective therapeutics to prevent or slow down AD, the most common cause of age-related dementia, will bear paramount significance in our endeavour to fight dementia. The hope is still living on that one day the anti-Aβ drugs currently under development will turn to effective AD-modifying therapeutics (Bachurin et al., 2017; Mullard, 2016, 2017; van Dyck, 2018). Nonetheless, the vast disappointments as a result of numerous flopped clinical trials of anti-Aβ drugs that have been witnessed over the recent few years call for urgent needs to gain a more comprehensive insight into the complicated aetiology of AD, identify new intervention targets and/or change the approaches to research and development of therapeutics (Goldman et al., 2018; Onyango, 2018; Rajendran and Paolicelli, 2018; Weinstein, 2018; Wes et al., 2016; White et al., 2017). As discussed in this review and highlighted in Fig. 5, the emerging evidence from recent studies leads to a novel 'hypothesis' that multiple TRPM2-mediated cellular and molecular mechanisms cascade Aβ and oxidative damage to AD pathologies. These new findings clearly support the multi-cellular hypothesis for AD pathogenesis and progression (Goetzl and Miller, 2017). In particular, the emerging role of the TRPM2 channel in sustaining a vicious positive feedback loop driving neuronal death and neuroinflammation may represent a potential pitfall that contributes to the poor therapeutic outcomes of anti-Aβ interventions alone in AD patients. The new findings or the 'hypothesis' based on such findings leads to the prospect of considering the TRPM2 channel as a novel drug target for intervening AD and age-related dementia.

The recent studies have no doubt made considerable progress in exposing the TRPM2 channel as a previously unrecognized mechanism for oxidative damage implicated in neurodegenerative diseases such as AD. Nevertheless, it is evident from the discussion presented above that more investigations are essential to evolve a better understanding of the TRPM2 channel nexus from Aβ and oxidative damage to AD pathogenesis and progression. It is well-known that Zn^{2+} is abundant in hippocampal neurons and can potently induce neuronal degeneration. TRPM2 channel activation is critical in ROS/Aβ-induced alterations in intracellular Zn^{2+} homeostasis, more specifically, lysosomal Zn^{2+} release and mitochondrial Zn^{2+} accumulation. However, direct evidence is still short to show how the TRPM2 channel is involved in such dynamic intracellular Zn^{2+} homeostasis in hippocampal neurons, whether the TRPM2 channel itself or TRPM2-dependent distinctive molecular mechanisms mediate Zn^{2+} flux from lysosomes or into mitochondria and, importantly, how such alterations in the Zn^{2+} homeostasis in these

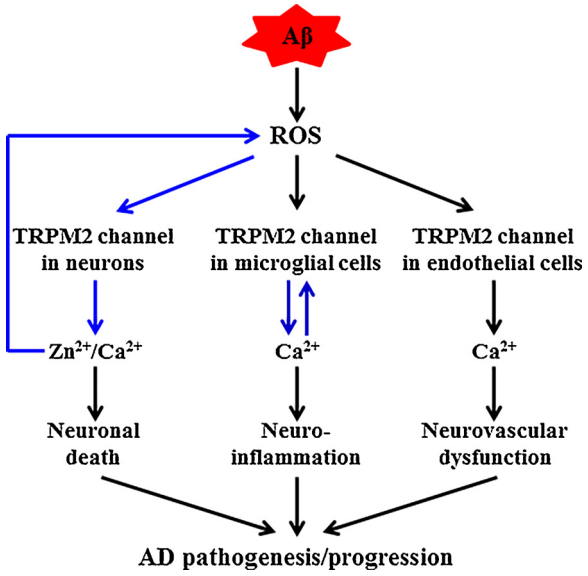

Fig. 5. Summary of the multiple cellular mechanisms that are mediated by the TRPM2 channel and contribute to Aβ-induced AD pathogenesis and/or progression.

Summary of the multiple cell mechanisms that contribute to Aβ-induced AD pathogenesis and progression. Aβ-induced ROS generation activates the TRPM2 channel in neurons, giving arise to alterations in the intracellular Ca^{2+}/Zn^{2+} homeostasis that drive neuronal death, or the TRPM2 channel in microglial cells resulting in an increase in the intracellular Ca^{2+} concentration that promotes generation of interleukin (IL)-1β and tumour necrosis factor (TNF)-α to cause neuroinflammation. The positive feedback loops for ROS generation in neurons and TRPM2 channel activation in neurons and microglial cells are indicated in blue lines. In addition, Aβ-induced ROS generation leads to TRPM2 channel activation in cerebral endothelial cells and TRPM2-mediated increase in the intracellular Ca^{2+} concentration and subsequent neurovascular dysfunction.

intracellular organelles disrupt their functions and lead to neuronal demise. Similarly, there is strong evidence from both *in vivo* and *in vitro* studies for the importance of the TRPM2 channel in Aβ-induced microglial cell activation. Moreover, *in vitro* studies show critical requirement of the TRPM2 channel for Aβ-induced generation of IL-1β and TNF-α. As pointed out above, IL-6 is another proinflammatory cytokine strongly implicated in Aβ-induced neuroinflammation for AD. The TRPM2 channel has been shown to be required for LPS-induced IL-6 generation from monocytes (Wehrhahn et al., 2010), but the role of the TRPM2 channel in IL-6 generation by microglial cells remains unknown. Further *in vivo* studies are needed to demonstrate that TRPM2-dependent generation of IL-1β and TNF-α are critically responsible for Aβ-induced neurotoxicity. The TRPM2 channel is also expressed in astrocyte, another type of glial cells in the brain that is also actively engaged in neuroinflammation (Leyns and Holtzman, 2017), but it remains poorly understood whether the TRPM2 channel in astrocytes contributes to Aβ-induced neuroinflammation. Our recent study shows that exposure to nanoparticles induced TRPM2-mediated cell death in pericytes *via* autophagy, leading to impairment in the BBB function (Jiang et al., 2017). It will be attractive to investigate whether Aβ, like nanoparticles, can also cause pericyte cell death and BBB disruption by inducing the TRPM2 channel activation, contributing to neurovascular function.

As introduced above, studies over the past few years have accumulated strong evidence to demonstrate or implicate a critical role for the TRPM2 channel in mediating a diversity of other oxidative stress-related conditions as well as AD, leading to growing interest in TRPM2 channel inhibitors. An increasing number of chemicals have been identified to inhibit the TRPM2 channel (Jiang et al., 2010). Recent examples include ADPR analogues (Luo et al., 2018; Moreau et al., 2013), curcumin (Kheradpezhouh et al., 2016), scalaradial (Starkus et al., 2017), tyrphostin AG and related compounds (Shimizu et al., 2014; Yamamoto et al., 2017) and tat-tagged M2NX peptide inhibitor (Shimizu et al., 2016), with some of them having been reported to exhibit selective inhibition towards the TRPM2 channel. Nevertheless, the pharmacology of the TRPM2 channel currently remains still limited. A majority of the recent studies have used genetic interventions in combination with rodent disease models, but it is therapeutically important to explore whether the human TRPM2 channel plays similar roles as have been revealed for the rodent TRPM2 channels. To this end, selective and potent TRPM2 channel inhibitors, particularly BBB-penetrable inhibitors, are highly desirable and prerequisite for providing the proof of concept that the human TRPM2 channel is a plausible target for AD therapeutics. With unceasing efforts in advancing our understanding of AD mechanisms, identifying new therapeutic targets and formulating drug development strategies, effective AD-modifying treatments are hoped to be within the reach of patients afflicted with debilitating conditions such as AD and dementia in the foreseeable future.

Declaration of competing interest

None.

Acknowledgements

The authors' own works described in this article were supported by grants from National Natural Science Foundation of China (31471118), Department of Education of Henan Province China (16IRTSTHN020), Wellcome Trust, Alzheimer's Research Trust, University of Leeds-Zhejiang University Strategic Collaboration Partnership Programme and Disciplinary Group of Psychology and Neuroscience Xinxiang Medical University (LHJ), and by University of Leeds-Chinese Scholar Council PhD scholarship (XL), Malaysian Governmental PhD Scholarship (SASM) and Royal Society fellowship (WY).

References

Abuarab, N., Munsey, T.S., Jiang, L.H., Li, J., Sivaprasadarao, A., 2017. High glucose-induced ROS activates TRPM2 to trigger lysosomal membrane permeabilization and Zn^{2+}-mediated mitochondrial fission. Sci. Signal. 10.

Akhiani, A.A., Werlenius, O., Aurelius, J., Movitz, C., Martner, A., Hellstrand, K., Thoren, F.B., 2014. Role of the ERK pathway for oxidant-induced parthanatos in human lymphocytes. PloS One 9, e89646.

Alam, Q., Alam, M.Z., Mushtaq, G., Damanhouri, G.A., Rasool, M., Kamal, M.A., Haque, A., 2016. Inflammatory process in Alzheimer's and Parkinson's diseases: central role of cytokines. Curr. Pharm. Des. 22, 541–548.

Alim, I., Teves, L., Li, R., Mori, Y., Tymianski, M., 2013. Modulation of NMDAR subunit expression by TRPM2 channels regulates neuronal vulnerability to ischemic cell death. J. Neurosci. 33, 17264–17277.

Alzheimer's Association Calcium Hypothesis, W, 2017. Calcium hypothesis of Alzheimer's disease and brain aging: a framework for integrating new evidence into a comprehensive theory of pathogenesis. Alzheimers Dement. 13 (178–182), e117.

Aminzadeh, M., Roghani, M., Sarfallah, A., Riazi, G.H., 2018. TRPM2 dependence of ROS-induced NLRP3 activation in Alzheimer's disease. Int. Immunopharmacol. 54, 78–85.

Autzen, H.E., Myasnikov, A.G., Campbell, M.G., Asarnow, D., Julius, D., Cheng, Y., 2018. Structure of the human TRPM4 ion channel in a lipid nanodisc. Science 359, 228–232.

Bachurin, S.O., Bovina, E.V., Ustyugov, A.A., 2017. Drugs in clinical trials for Alzheimer's disease: the major trends. Med. Res. Rev. 37, 1186–1225.

Bai, J.Z., Lipski, J., 2010. Differential expression of TRPM2 and TRPV4 channels and their potential role in oxidative stress-induced cell death in organotypic hippocampal culture. Neurotoxicology 31, 204–214.

Beck, A., Kolisek, M., Bagley, L.A., Fleig, A., Penner, R., 2006. Nicotinic acid adenine dinucleotide phosphate and cyclic ADP-ribose regulate TRPM2 channels in T lymphocytes. FASEB J. 20, 962–964.

Belrose, J.C., Jackson, M.F., 2018. TRPM2: a candidate therapeutic target for treating neurological diseases. Acta. Pharmacol. Sin. 39, 722–732.

Belrose, J.C., Xie, Y.F., Gierszewski, L.J., MacDonald, J.F., Jackson, M.F., 2012. Loss of glutathione homeostasis associated with neuronal senescence facilitates TRPM2 channel activation in cultured hippocampal pyramidal neurons. Mol. Brain 5, 11.

Berridge, M.J., 2010. Calcium hypothesis of Alzheimer's disease. Pflugers Arch. 459, 441–449.

Berridge, M.J., Bootman, M.D., Roderick, H.L., 2003. Calcium signalling: dynamics,

homeostasis and remodelling. Nat. Rev. Mol. Cell Biol. 4, 517–529.
Bhat, A.H., Dar, K.B., Anees, S., Zargar, M.A., Masood, A., Sofi, M.A., Ganie, S.A., 2015. Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; A mechanistic insight. Biomed. Pharmacother. 74, 101–110.
Blennow, K., Hampel, H., Weiner, M., Zetterberg, H., 2010. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat. Rev. Neurol. 6, 131–144.
Block, M.L., Zecca, L., Hong, J.S., 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat. Rev. Neurosci. 8, 57–69.
Borchelt, D.R., Ratovitski, T., van Lare, J., Lee, M.K., Gonzales, V., Jenkins, N.A., Copeland, N.G., Price, D.L., Sisodia, S.S., 1997. Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. Neuron 19, 939–945.
Buelow, B., Song, Y., Scharenberg, A.M., 2008. The poly(ADP-ribose) polymerase PARP-1 is required for oxidative stress-induced TRPM2 activation in lymphocytes. J. Biol. Chem. 283, 24571–24583.
Butterfield, D.A., 2018. Perspectives on oxidative stress in Alzheimer's disease and predictions of future research emphases. J. Alzheimer. Dis. 64, S469–S479.
Butterfield, D.A., Boyd-Kimball, D., 2018. Oxidative stress, amyloid-beta peptide, and altered key molecular pathways in the pathogenesis and progression of Alzheimer's disease. J. Alzheimer. Dis. 62, 1345–1367.
Cao, E., Liao, M., Cheng, Y., Julius, D., 2013. TRPV1 structures in distinct conformations reveal activation mechanisms. Nature 504, 113–118.
Chung, K.K., Freestone, P.S., Lipski, J., 2011. Expression and functional properties of TRPM2 channels in dopaminergic neurons of the substantia nigra of the rat. J. Neurophysiol. 106, 2865–2875.
Clapham, D.E., 2003. TRP channels as cellular sensors. Nature 426, 517–524.
Colonna, M., Butovsky, O., 2017. Microglia function in the central nervous system during health and neurodegeneration. Ann. Rev. Immunol. 35, 441–468.
Corona, C., Pensalfini, A., Frazzini, V., Sensi, S.L., 2011. New therapeutic targets in Alzheimer's disease: brain deregulation of calcium and zinc. Cell Death Dis. 2, e176.
Deng, Z., Paknejad, N., Maksaev, G., Sala-Rabanal, M., Nichols, C.G., Hite, R.K., Yuan, P., 2018. Cryo-EM and X-ray structures of TRPV4 reveal insight into ion permeation and gating mechanisms. Nat. Struct. Mol. Biol. 25, 252–260.
Doll, D.N., Rellick, S.L., Barr, T.L., Ren, X., Simpkins, J.W., 2015. Rapid mitochondrial dysfunction mediates TNF-alpha-induced neurotoxicity. J. Neurochem. 132, 443–451.
Domercq, M., Mato, S., Soria, F.N., Sanchez-gomez, M.V., Alberdi, E., Matute, C., 2013. Zn^{2+}-induced ERK activation mediates PARP-1-dependent ischemic-reoxygenation damage to oligodendrocytes. Glia 61, 383–393.
Du, J., Xie, J., Yue, L., 2009. Intracellular calcium activates TRPM2 and its alternative spliced isoforms. Proc. Natl. Acad. Sci. USA. 106, 7239–7244.
Duan, J., Li, Z., Li, J., Santa-Cruz, A., Sanchez-Martinez, S., Zhang, J., Clapham, D.E., 2018. Structure of full-length human TRPM4. Proc. Natl. Acad. Sci. U.S.A. 115, 2377–2382.
Fan, C., Choi, W., Sun, W., Du, J., Lu, W., 2018. Structure of the human lipid-gated cation channel TRPC3. Elife 7, e36852.
Feng, S., Li, H., Tai, Y., Huang, J., Su, Y., Abramowitz, J., Zhu, M.X., Birnbaumer, L., Wang, Y., 2013. Canonical transient receptor potential 3 channels regulate mitochondrial calcium uptake. Proc. Natl. Acad. Sci. U.S.A. 110, 11011–11016.
Fleig, A., Penner, R., 2004. The TRPM ion channel subfamily: molecular, biophysical and functional features. Trends Pharmacol. Sci. 25, 633–639.
Fliegert, R., Bauche, A., Wolf Perez, A.M., Watt, J.M., Rozewitz, M.D., Winzer, R., Janus, M., Gu, F., Rosche, A., Harneit, A., Flato, M., Moreau, C., Kirchberger, T., Wolters, V., Potter, B.V.L., Guse, A.H., 2017a. 2'-Deoxyadenosine 5'-diphosphoribose is an endogenous TRPM2 superagonist. Nat. Chem. Biol. 13, 1036–1044.
Fliegert, R., Watt, J.M., Schobel, A., Rozewitz, M.D., Moreau, C., Kirchberger, T., Thomas, M.P., Sick, W., Araujo, A.C., Harneit, A., Potter, B.V.L., Guse, A.H., 2017b. Ligand-induced activation of human TRPM2 requires the terminal ribose of ADPR and involves Arg1433 and Tyr1349. Biochem. J. 474, 2159–2175.
Fonfria, E., Marshall, I.C., Benham, C.D., Boyfield, I., Brown, J.D., Hill, K., Hughes, J.P., Skaper, S.D., McNulty, S., 2004. TRPM2 channel opening in response to oxidative stress is dependent on activation of poly(ADP-ribose) polymerase. Br. J. Pharmacol. 143, 186–192.
Fonfria, E., Marshall, I.C., Boyfield, I., Skaper, S.D., Hughes, J.P., Owen, D.E., Zhang, W., Miller, B.A., Benham, C.D., McNulty, S., 2005. Amyloid beta-peptide (1-42) and hydrogen peroxide-induced toxicity are mediated by TRPM2 in rat primary striatal cultures. J. Neurochem. 95, 715–723.
Fujiwara, Y., Minor, D.L., Jr, 2008. X-ray crystal structure of a TRPM assembly domain reveals an antiparallel four-stranded coiled-coil. J. Mol. Biol. 383, 854–870.
Fukui, H., Moraes, C.T., 2008. The mitochondrial impairment, oxidative stress and neurodegeneration connection: reality or just an attractive hypothesis? Trends Neurosci. 31, 251–256.
Gao, G., Wang, W., Tadagavadi, R.K., Briley, N.E., Love, M.I., Miller, B.A., Reeves, W.B., 2014. TRPM2 mediates ischemic kidney injury and oxidant stress through RAC1. J. Clin. Invest. 124, 4989–5001.
Gelderblom, M., Melzer, N., Schattling, B., Gob, E., Hicking, G., Arunachalam, P., Bittner, S., Ufer, F., Herrmann, A.M., Bernreuther, C., Glatzel, M., Gerloff, C., Kleinschnitz, C., Meuth, S.G., Friese, M.A., Magnus, T., 2014. Transient receptor potential melastatin subfamily member 2 cation channel regulates detrimental immune cell invasion in ischemic stroke. Stroke 45, 3395–3402.
Glass, C.K., Saijo, K., Winner, B., Marchetto, M.C., Gage, F.H., 2010. Mechanisms underlying inflammation in neurodegeneration. Cell 140, 918–934.
Goetzl, E.J., Miller, B.L., 2017. Multicellular hypothesis for the pathogenesis of Alzheimer's disease. FASEB J. 31, 1792–1795.
Goldman, D.P., Fillit, H., Neumann, P., 2018. Accelerating Alzheimer's disease drug innovations from the research pipeline to patients. Alzheimers Dement. 14, 833–836.
Gong, T., Yang, Y., Jin, T., Jiang, W., Zhou, R., 2018. Orchestration of NLRP3 inflammasome activation by ion fluxes. Trends Immunol. 39, 393–406.
Grubisha, O., Rafty, L.A., Takanishi, C.L., Xu, X., Tong, L., Perraud, A.L., Scharenberg, A.M., Denu, J.M., 2006. Metabolite of SIR2 reaction modulates TRPM2 ion channel. J. Biol. Chem. 281, 14057–14065.
Guillot-Sestier, M.V., Doty, K.R., Town, T., 2015. Innate immunity fights Alzheimer's disease. Trends Neurosci. 38, 674–681.
Guo, J., She, J., Zeng, W., Chen, Q., Bai, X.C., Jiang, Y., 2017. Structures of the calcium-activated, non-selective cation channel TRPM4. Nature 552, 205–209.
Hafner-Bratkovic, I., Pelegrin, P., 2018. Ion homeostasis and ion channels in NLRP3 inflammasome activation and regulation. Curr. Opin. Immunol. 52, 8–17.
Hara, Y., Wakamori, M., Ishii, M., Maeno, E., Nishida, M., Yoshida, T., Yamada, H., Shimizu, S., Mori, E., Kudoh, J., Shimizu, N., Kurose, H., Okada, Y., Imoto, K., Mori, Y., 2002. LTRPC2 Ca^{2+}-permeable channel activated by changes in redox status confers susceptibility to cell death. Mol. Cell 9, 163–173.
Hardy, J., Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297, 353–356.
He, P., Zhong, Z., Lindholm, K., Berning, L., Lee, W., Lemere, C., Staufenbiel, M., Li, R., Shen, Y., 2007. Deletion of tumor necrosis factor death receptor inhibits amyloid beta generation and prevents learning and memory deficits in Alzheimer's mice. J. Cell Biol. 178, 829–841.
Hecquet, C.M., Ahmmed, G.U., Vogel, S.M., Malik, A.B., 2008. Role of TRPM2 channel in mediating H_2O_2-induced Ca^{2+} entry and endothelial hyperpermeability. Circ. Res. 102, 347–355.
Hecquet, C.M., Zhang, M., Mittal, M., Vogel, S.M., Di, A., Gao, X., Bonini, M.G., Malik, A.B., 2014. Cooperative interaction of trp melastatin channel transient receptor potential (TRPM2) with its splice variant TRPM2 short variant is essential for endothelial cell apoptosis. Circ. Res. 114, 469–479.
Heiner, I., Eisfeld, J., Halaszovich, C.R., Wehage, E., Jungling, E., Zitt, C., Luckhoff, A., 2003. Expression profile of the transient receptor potential (TRP) family in neutrophil granulocytes: evidence for currents through long TRP channel 2 induced by ADP-ribose and NAD. Biochem. J. 371, 1045–1053.
Heneka, M.T., Kummer, M.P., Stutz, A., Delekate, A., Schwartz, S., Vieira-Saecker, A., Griep, A., Axt, D., Remus, A., Tzeng, T.C., Gelpi, E., Halle, A., Korte, M., Latz, E., Golenbock, D.T., 2013. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 493, 674–678.
Heneka, M.T., Kummer, M.P., Latz, E., 2014. Innate immune activation in neurodegenerative disease. Nat. Rev. Immunol 14, 463–477.
Heneka, M.T., Carson, M.J., El Khoury, J., Landreth, G.E., Brosseron, F., Feinstein, D.L., Jacobs, A.H., Wyss-Coray, T., Vitorica, J., Ransohoff, R.M., Herrup, K., Frautschy, S.A., Finsen, B., Brown, G.C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., Petzold, G.C., Town, T., Morgan, D., Shinohara, M.L., Perry, V.H., Holmes, C., Bazan, N.G., Brooks, D.J., Hunot, S., Joseph, B., Deigendesch, N., Garaschuk, O., Boddeke, E., Dinarello, C.A., Breitner, J.C., Cole, G.M., Golenbock, D.T., Kummer, M.P., 2015. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 14, 388–405.
Heppner, F.L., Ransohoff, R.M., Becher, B., 2015. Immune attack: the role of inflammation in Alzheimer disease. Nat. Rev. Neurosci. 16, 358–372.
Hill, K., Tigue, N.J., Kelsell, R.E., Benham, C.D., McNulty, S., Schaefer, M., Randall, A.D., 2006. Characterisation of recombinant rat TRPM2 and a TRPM2-like conductance in cultured rat striatal neurones. Neuropharmacology 50, 89–97.
Hirschi, M., Herzik Jr, M.A., Wie, J., Suo, Y., Borschel, W.F., Ren, D., Lander, G.C., Lee, S.Y., 2017. Cryo-electron microscopy structure of the lysosomal calcium-permeable channel TRPML3. Nature 550, 411–414.
Hong, S., Stevens, B., 2016. Microglia: phagocytosing to clear, sculpt, and eliminate. Dev. Cell 38, 126–128.
Hong, S., Dissing-Olesen, L., Stevens, B., 2016. New insights on the role of microglia in synaptic pruning in health and disease. Curr. Opin. Neurobiol. 36, 128–134.
Honig, L.S., Vellas, B., Woodward, M., Boada, M., Bullock, R., Borrie, M., Hager, K., Andreasen, N., Scarpini, E., Liu-Seifert, H., Case, M., Dean, R.A., Hake, A., Sundell, K., Poole Hoffmann, V., Carlson, C., Khanna, R., Mintun, M., DeMattos, R., Selzler, K.J., Siemers, E., 2018. Trial of solanezumab for mild dementia due to Alzheimer's disease. N. Engl. J. Med. 378, 321–330.
Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., Yang, F., Cole, G., 1996. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science 274, 99–102.
Huang, S., Turlova, E., Li, F., Bao, M.H., Szeto, V., Wong, R., Abussaud, A., Wang, H., Zhu, S., Gao, X., Mori, Y., Feng, Z.P., Sun, H.S., 2017. Transient receptor potential melastatin 2 channels (TRPM2) mediate neonatal hypoxic-ischemic brain injury in mice. Exp. Neurol. 296, 32–40.
Hughes, T.E.T., Lodowski, D.T., Huynh, K.W., Yazici, A., Del Rosario, J., Kapoor, A., Basak, S., Samanta, A., Han, X., Chakrapani, S., Zhou, Z.H., Filizola, M., Rohacs, T., Han, S., Moiseenkova-Bell, V.Y., 2018. Structural basis of TRPV5 channel inhibition by econazole revealed by cryo-EM. Nat. Struct. Mol. Biol. 25, 53–60.
Huynh, K.W., Cohen, M.R., Jiang, J., Samanta, A., Lodowski, D.T., Zhou, Z.H., Moiseenkova-Bell, V.Y., 2016. Structure of the full-length TRPV2 channel by cryo-EM. Nat. Commun. 7, 11130.
Hwang, J.J., Lee, S.J., Kim, T.Y., Cho, J.H., Koh, J.Y., 2008. Zinc and 4-hydroxy-2-nonenal mediate lysosomal membrane permeabilization induced by H_2O_2 in cultured hippocampal neurons. J Neurosci. 28, 3114–3122.
Iadecola, C., 2013. The pathobiology of vascular dementia. Neuron 80, 844–866.
Iadecola, C., 2017. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron 96, 17–42.
Janelsins, M.C., Mastrangelo, M.A., Park, K.M., Sudol, K.L., Narrow, W.C., Oddo, S., LaFerla, F.M., Callahan, L.M., Federoff, H.J., Bowers, W.J., 2008. Chronic neuron-specific tumor necrosis factor-alpha expression enhances the local inflammatory environment ultimately leading to neuronal death in 3xTg-AD mice. Am. J. Pathol.

173, 1768–1782.
Jang, Y., Lee, S.H., Lee, B., Jung, S., Khalid, A., Uchida, K., Tominaga, M., Jeon, D., Oh, U., 2015. TRPM2, a susceptibility gene for bipolar disorder, regulates glycogen synthase kinase-3 activity in the brain. J. Neurosci. 35, 11811–11823.
Jankowsky, J.L., Xu, G., Fromholt, D., Gonzales, V., Borchelt, D.R., 2003. Environmental enrichment exacerbates amyloid plaque formation in a transgenic mouse model of Alzheimer disease. J. Neuropathol. Exp. Neurol. 62, 1220–1227.
Jankowsky, J.L., Zheng, H., 2017. Practical considerations for choosing a mouse model of Alzheimer's disease. Mol. Neurodegener. 12, 89.
Jeong, H., Kim, Y.H., Lee, Y., Jung, S.J., Oh, S.B., 2017. TRPM2 contributes to LPC-induced intracellular Ca^{2+} influx and microglial activation. Biochem. Biophys. Res. Commun. 485, 301–306.
Ji, S.G., Weiss, J.H., 2018. Zn^{2+}-induced disruption of neuronal mitochondrial function: synergism with Ca^{2+}, critical dependence upon cytosolic Zn^{2+} buffering, and contributions to neuronal injury. Exp. Neurol. 302, 181–195.
Jia, J., Verma, S., Nakayama, S., Quillinan, N., Grafe, M.R., Hurn, P.D., Herson, P.S., 2011. Sex differences in neuroprotection provided by inhibition of TRPM2 channels following experimental stroke. J. Cereb. Blood Flow Metab. 31, 2160–2168.
Jiang, L.H., 2007. Subunit interaction in channel assembly and functional regulation of transient receptor potential melastatin (TRPM) channels. Biochem. Soc. Trans. 35, 86–88.
Jiang, L.H., Yang, W., Zou, J., Beech, D.J., 2010. TRPM2 channel properties, functions and therapeutic potentials. Expert. Opin. Ther. Targets 14, 973–988.
Jiang, T., Sun, Q., Chen, S., 2016. Oxidative stress: a major pathogenesis and potential therapeutic target of antioxidative agents in Parkinson's disease and Alzheimer's disease. Prog. Neurobiol. 147, 1–19.
Jiang, Q., Gao, Y., Wang, C., Tao, R., Wu, Y., Zhan, K., Liao, M., Lu, N., Lu, Y., Wilcox, C.S., Luo, J., Jiang, L.H., Yang, W., Han, F., 2017. Nitration of TRPM2 as a molecular switch induces autophagy during brain pericyte injury. Antioxid. Redox. Signal. 27, 1297–1316.
Kalliolias, G.D., Ivashkiv, L.B., 2016. TNF biology, pathogenic mechanisms and emerging therapeutic strategies. Nat. Rev. Rheumatol. 12, 49–62.
Kaneko, S., Kawakami, S., Hara, Y., Wakamori, M., Itoh, E., Minami, T., Takada, Y., Kume, T., Katsuki, H., Mori, Y., Akaike, A., 2006. A critical role of TRPM2 in neuronal cell death by hydrogen peroxide. J. Pharmacol. Sci. 101, 66–76.
Kauppinen, T.M., Chan, W.Y., Suh, S.W., Wiggins, A.K., Huang, E.J., Swanson, R.A., 2006. Direct phosphorylation and regulation of poly(ADP-ribose) polymerase-1 by extracellular signal-regulated kinases 1/2. Proc. Natl. Acad. Sci. U.S.A. 103, 7136–7141.
Kerr, J.S., Adriaanse, B.A., Greig, N.H., Mattson, M.P., Cader, M.Z., Bohr, V.A., Fang, E.F., 2017. Mitophagy and Alzheimer's disease: cellular and molecular mechanisms. Trends Neurosci. 40, 151–166.
Kheradpezhouh, E., Ma, L., Morphett, A., Barritt, G.J., Rychkov, G.Y., 2014. TRPM2 channels mediate acetaminophen-induced liver damage. Proc. Natl. Acad. Sci. U.S.A. 111, 3176–3181.
Kheradpezhouh, E., Barritt, G.J., Rychkov, G.Y., 2016. Curcumin inhibits activation of TRPM2 channels in rat hepatocytes. Redox Biol. 7, 1–7.
Knowles, H., Li, Y., Perraud, A.L., 2013. The TRPM2 ion channel, an oxidative stress and metabolic sensor regulating innate immunity and inflammation. Immunol. Res. 55, 241–248.
Koizumi, K., Wang, G., Park, L., 2016. Endothelial dysfunction and amyloid-beta-induced neurovascular alterations. Cell. Mol. Neurobiol. 36, 155–165.
Kolisek, M., Beck, A., Fleig, A., Penner, R., 2005. Cyclic ADP-ribose and hydrogen peroxide synergize with ADP-ribose in the activation of TRPM2 channels. Mol. Cell 18, 61–69.
Kraft, R., Grimm, C., Grosse, K., Hoffmann, A., Sauerbruch, S., Kettenmann, H., Schultz, G., Harteneck, C., 2004. Hydrogen peroxide and ADP-ribose induce TRPM2-mediated calcium influx and cation currents in microglia. Am. J. Physiol. Cell Physiol. 286, C129–137.
Kuhn, F.J., Luckhoff, A., 2004. Sites of the NUDT9-H domain critical for ADP-ribose activation of the cation channel TRPM2. J. Biol. Chem. 279, 46431–46437.
Kuhn, F., Kuhn, C., Luckhoff, A., 2017. Different principles of ADP-ribose-mediated activation and opposite roles of the NUDT9 homology domain in the TRPM2 orthologs of man and sea anemone. Front. Physiol 8, 879.
Kumar, D., Ganeshpurkar, A., Kumar, D., Modi, G., Gupta, S.K., Singh, S.K., 2018. Secretase inhibitors for the treatment of Alzheimer's disease: long road ahead. Eur. J. Med. Chem. 148, 436–452.
LaFerla, F.M., 2002. Calcium dyshomeostasis and intracellular signalling in Alzheimer's disease. Nat. Rev. Neurosci. 3, 862–872.
Lange, I., Yamamoto, S., Partida-Sanchez, S., Mori, Y., Fleig, A., Penner, R., 2009. TRPM2 functions as a lysosomal Ca^{2+}-release channel in beta cells. Sci. Signal 2, ra23.
Lee, M., Cho, T., Jantaratnotai, N., Wang, Y.T., McGeer, E., McGeer, P.L., 2010. Depletion of GSH in glial cells induces neurotoxicity: relevance to aging and degenerative neurological diseases. FASEB J. 24, 2533–2545.
Leyns, C.E.G., Holtzman, D.M., 2017. Glial contributions to neurodegeneration in tauopathies. Mol. Neurodegener. 12, 50.
Li, X., Jiang, L.H., 2018. Multiple molecular mechanisms form a positive feedback loop driving amyloid beta42 peptide-induced neurotoxicity via activation of the TRPM2 channel in hippocampal neurons. Cell Death Dis. 9, 195.
Li, C., Meng, L., Li, X., Li, D., Jiang, L.H., 2015. Non-NMDAR neuronal Ca^{2+}-permeable channels in delayed neuronal death and as potential therapeutic targets for ischemic brain damage. Expert. Opin. Ther. Targets 19, 879–892.
Li, J., Gao, Y., Bao, X., Li, F., Yao, W., Feng, Z., Yin, Y., 2017a. TRPM2: a potential drug target to retard oxidative stress. Front. Biosci. 22, 1427–1438.
Li, X., Yang, W., Jiang, L.H., 2017b. Alteration in intracellular Zn^{2+} homeostasis as a result of TRPM2 channel activation contributes to ROS-induced hippocampal neuronal death. Front. Mol. Neurosci. 10, 414.
Liao, M., Cao, E., Julius, D., Cheng, Y., 2013. Structure of the TRPV1 ion channel determined by electron cryo-microscopy. Nature 504, 107–112.
Liu, B., Hong, J.S., 2003. Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention. J. Pharmacol. Exp. Ther. 304, 1–7.
Luo, X., Li, M., Zhan, K., Yang, W., Zhang, L., Wang, K., Yu, P., Zhang, L., 2018. Selective inhibition of TRPM2 channel by two novel synthesized ADPR analogues. Chem. Biol. Drug Des. 91, 552–566.
Manna, P.T., Munsey, T.S., Abuarab, N., Li, F., Asipu, A., Howell, G., Sedo, A., Yang, W., Naylor, J., Beech, D.J., Jiang, L.H., Sivaprasadarao, A., 2015. TRPM2-mediated intracellular Zn^{2+} release triggers pancreatic beta-cell death. Biochem. J. 466, 537–546.
Maruszak, A., Zekanowski, C., 2011. Mitochondrial dysfunction and Alzheimer's disease. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 320–330.
Mattson, M.P., Gleichmann, M., Cheng, A., 2008. Mitochondria in neuroplasticity and neurological disorders. Neuron 60, 748–766.
McDade, E., Kim, A., James, J., Sheu, L.K., Kuan, D.C., Minhas, D., Gianaros, P.J., Ikonomovic, S., Lopez, O., Snitz, B., Price, J., Becker, J., Mathis, C., Klunk, W., 2014. Cerebral perfusion alterations and cerebral amyloid in autosomal dominant Alzheimer disease. Neurology 83, 710–717.
McManus, M.J., Murphy, M.P., Franklin, J.L., 2011. The mitochondria-targeted antioxidant MitoQ prevents loss of spatial memory retention and early neuropathology in a transgenic mouse model of Alzheimer's disease. J. Neurosci. 31, 15703–15715.
Mederos y Schnitzler, M., Waring, J., Gudermann, T., Chubanov, V., 2008. Evolutionary determinants of divergent calcium selectivity of TRPM channels. FASEB J. 22, 1540–1551.
Mei, Z.Z., Xia, R., Beech, D.J., Jiang, L.H., 2006. Intracellular coiled-coil domain engaged in subunit interaction and assembly of melastatin-related transient receptor potential channel 2. J. Biol. Chem. 281, 38748–38756.
Miller, B.A., Zhang, W., 2011. TRP channels as mediators of oxidative stress. Adv. Exp. Med. Biol. 704, 531–544.
Minter, M.R., Taylor, J.M., Crack, P.J., 2016. The contribution of neuroinflammation to amyloid toxicity in Alzheimer's disease. J. Neurochem. 136, 457–474.
Mittal, M., Nepal, S., Tsukasaki, Y., Hecquet, C.M., Soni, D., Rehman, J., Tiruppathi, C., Malik, A.B., 2018. Neutrophil activation of endothelial cell-expressed TRPM2 mediates transendothelial neutrophil migration and vascular injury. Circ. Res. 121, 1081–1091.
Miyake, T., Shirakawa, H., Kusano, A., Sakimoto, S., Konno, M., Nakagawa, T., Mori, Y., Kaneko, S., 2014. TRPM2 contributes to LPS/IFNgamma-induced production of nitric oxide via the p38/JNK pathway in microglia. Biochem. Biophys. Res. Commun. 444, 212–217.
Miyanohara, J., Kakae, M., Nagayasu, K., Nakagawa, T., Mori, Y., Arai, K., Shirakawa, H., Kaneko, S., 2018. TRPM2 channel aggravates CNS inflammation and cognitive impairment via activation of microglia in chronic cerebral hypoperfusion. J. Neurosci. 38, 3520–3533.
Moreau, C., Kirchberger, T., Swarbrick, J.M., Bartlett, S.J., Fliegert, R., Yorgan, T., Bauche, A., Harneit, A., Guse, A.H., Potter, B.V., 2013. Structure-activity relationship of adenosine 5'-diphosphoribose at the transient receptor potential melastatin 2 (TRPM2) channel: rational design of antagonists. J. Med. Chem. 56, 10079–10102.
Mosher, K.I., Wyss-Coray, T., 2014. Microglial dysfunction in brain aging and Alzheimer's disease. Biochem. Pharmacol. 88, 594–604.
Mullard, A., 2016. Alzheimer amyloid hypothesis lives on. Nat. Rev. Drug Discov. 16, 3–5.
Mullard, A., 2017. BACE inhibitor bust in Alzheimer trial. Nat. Rev. Drug Discov. 16, 155.
Nagamine, K., Kudoh, J., Minoshima, S., Kawasaki, K., Asakawa, S., Ito, F., Shimizu, N., 1998. Molecular cloning of a novel putative Ca^{2+} channel protein (TRPC7) highly expressed in brain. Genomics 54, 124–131.
Nakayama, S., Vest, R., Traystman, R.J., Herson, P.S., 2013. Sexually dimorphic response of TRPM2 inhibition following cardiac arrest-induced global cerebral ischemia in mice. J. Mol. Neurosci. 51, 92–98.
Nayernia, Z., Jaquet, V., Krause, K.H., 2014. New insights on NOX enzymes in the central nervous system. Antioxid. Redox Signal. 20, 2815–2837.
Nilius, B., 2007. TRP channels in disease. Biochim. Biophys. Acta 1772, 805–812.
Nussbaum, R.L., Ellis, C.E., 2003. Alzheimer's disease and Parkinson's disease. N. Engl. J. Med. 348, 1356–1364.
Oakley, H., Cole, S.L., Logan, S., Maus, E., Shao, P., Craft, J., Guillozet-Bongaarts, A., Ohno, M., Disterhoft, J., Van Eldik, L., Berry, R., Vassar, R., 2006. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J. Neurosci. 26, 10129–10140.
Oddo, S., Caccamo, A., Shepherd, J.D., Murphy, M.P., Golde, T.E., Kayed, R., Metherate, R., Mattson, M.P., Akbari, Y., LaFerla, F.M., 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 39, 409–421.
Olah, M.E., Jackson, M.F., Li, H., Perez, Y., Sun, H.S., Kiyonaka, S., Mori, Y., Tymianski, M., MacDonald, J.F., 2009. Ca^{2+}-dependent induction of TRPM2 currents in hippocampal neurons. J. Physiol. 587, 965–979.
Onyango, I.G., 2018. Modulation of mitochondrial bioenergetics as a therapeutic strategy in Alzheimer's disease. Neural. Regen. Res. 13, 19–25.
Ostapchenko, V.G., Chen, M., Guzman, M.S., Xie, Y.F., Lavine, N., Fan, J., Beraldo, F.H., Martyn, A.C., Belrose, J.C., Mori, Y., MacDonald, J.F., Prado, V.F., Prado, M.A., Jackson, M.F., 2015. The rransient receptor potential melastatin 2 (TRPM2) channel contributes to beta-amyloid oligomer-related neurotoxicity and memory impairment. J. Neurosci. 35, 15157–15169.
Overk, C., Masliah, E., 2017. Perspective on the calcium dyshomeostasis hypothesis in the pathogenesis of selective neuronal degeneration in animal models of Alzheimer's disease. Alzheimers Dement. 13, 183–185.

Paouri, E., Tzara, O., Zenelak, S., Georgopoulos, S., 2017. Genetic deletion of tumor necrosis factor-alpha attenuates amyloid-beta production and decreases amyloid plaque formation and glial response in the 5XFAD model of Alzheimer's disease. J. Alzheimer. Dis. 60, 165–181.
Park, L., Wang, G., Moore, J., Girouard, H., Zhou, P., Anrather, J., Iadecola, C., 2014. The key role of transient receptor potential melastatin-2 channels in amyloid-beta-induced neurovascular dysfunction. Nat. Commun. 5, 5318.
Paulsen, C.E., Armache, J.P., Gao, Y., Cheng, Y., Julius, D., 2015. Structure of the TRPA1 ion channel suggests regulatory mechanisms. Nature 520, 511–517.
Perraud, A.L., Fleig, A., Dunn, C.A., Bagley, L.A., Launay, P., Schmitz, C., Stokes, A.J., Zhu, Q., Bessman, M.J., Penner, R., Kinet, J.P., Scharenberg, A.M., 2001. ADP-ribose gating of the calcium-permeable LTRPC2 channel revealed by Nudix motif homology. Nature 411, 595–599.
Perraud, A.L., Takanishi, C.L., Shen, B., Kang, S., Smith, M.K., Schmitz, C., Knowles, H.M., Ferraris, D., Li, W., Zhang, J., Stoddard, B.L., Scharenberg, A.M., 2005. Accumulation of free ADP-ribose from mitochondria mediates oxidative stress-induced gating of TRPM2 cation channels. J. Biol. Chem. 280, 6138–6148.
Perry, V.H., Holmes, C., 2014. Microglial priming in neurodegenerative disease. Nat. Rev. Neurol. 10, 217–224.
Prokop, S., Miller, K.R., Heppner, F.L., 2013. Microglia actions in Alzheimer's disease. Acta Neuropathol. 126, 461–477.
Purnell, C., Gao, S., Callahan, C.M., Hendrie, H.C., 2009. Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. Alzheimer Dis Assoc. Disord. 23, 1–10.
Rajendran, L., Paolicelli, R.C., 2018. Microglia-mediated synapse loss in Alzheimer's disease. J. Neurosci. 38, 2911–2919.
Ransohoff, R.M., 2016. How neuroinflammation contributes to neurodegeneration. Science 353, 777–783.
Ru, X., Yao, X., 2014. TRPM2: a multifunctional ion channel for oxidative stress sensing. Acta Physiol. Sinica 66, 7–15.
Sano, Y., Inamura, K., Miyake, A., Mochizuki, S., Yokoi, H., Matsushime, H., Furuichi, K., 2001. Immunocyte Ca^{2+} influx system mediated by LTRPC2. Science 293, 1327–1330.
Selkoe, D.J., Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med. 8, 595–608.
Shimizu, T., Macey, T.A., Quillinan, N., Klawitter, J., Perraud, A.L., Traystman, R.J., Herson, P.S., 2013. Androgen and PARP-1 regulation of TRPM2 channels after ischemic injury. J. Cereb. Blood Flow Metab. 33, 1549–1555.
Shimizu, S., Yonezawa, R., Hagiwara, T., Yoshida, T., Takahashi, N., Hamano, S., Negoro, T., Toda, T., Wakamori, M., Mori, Y., Ishii, M., 2014. Inhibitory effects of AG490 on H2O2-induced TRPM2-mediated Ca^{2+} entry. Eur. J. Pharmacol. 742, 22–30.
Shimizu, T., Dietz, R.M., Cruz-Torres, I., Strnad, F., Garske, A.K., Moreno, M., Venna, V.R., Quillinan, N., Herson, P.S., 2016. Extended therapeutic window of a novel peptide inhibitor of TRPM2 channels following focal cerebral ischemia. Exp. Neurol. 283, 151–156.
Shuttleworth, C.W., Weiss, J.H., 2011. Zinc: new clues to diverse roles in brain ischemia. Trends Pharmacol. Sci. 32, 480–486.
Smith, M.A., Perry, G., Richey, P.L., Sayre, L.M., Anderson, V.E., Beal, M.F., Kowall, N., 1996. Oxidative damage in Alzheimer's. Nature 382, 120–121.
Smith, M.A., Herson, P.S., Lee, K., Pinnock, R.D., Ashford, M.L., 2003. Hydrogen-peroxide-induced toxicity of rat striatal neurones involves activation of a non-selective cation channel. J. Physiol. 547, 417–425.
Song, L., Pei, L., Yao, S., Wu, Y., Shang, Y., 2017. NLRP3 inflammasome in neurological diseases, from functions to therapies. Front. Cell. Neurosci. 11, 63.
Spangenberg, E.E., Green, K.N., 2017. Inflammation in Alzheimer's disease: lessons learned from microglia-depletion models. Brain Behav. Immun. 61, 1–11.
Starkus, J.G., Poerzgen, P., Layugan, K., Kawabata, K.G., Goto, J.I., Suzuki, S., Myers, G., Kelly, M., Penner, R., Fleig, A., Horgen, F.D., 2017. Scalaradial is a potent inhibitor of transient receptor potential melastatin 2 (TRPM2) ion channels. J. Nat. Prod. 80, 2741–2750.
Sturchler-Pierrat, C., Abramowski, D., Duke, M., Wiederhold, K.H., Mistl, C., Rothacher, S., Ledermann, B., Bürki, K., Frey, P., Paganetti, P.A., Waridel, C., Calhoun, M.E., Jucker, M., Probst, A., Staufenbiel, M., Sommer, B., 1997. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. Proc. Natl. Acad. Sci. U. S. A. 94, 13287–13292.
Sumoza-Toledo, A., Penner, R., 2011. TRPM2: a multifunctional ion channel for calcium signalling. J. Physiol. 589, 1515–1525.
Sumoza-Toledo, A., Lange, I., Cortado, H., Bhagat, H., Mori, Y., Fleig, A., Penner, R., Partida-Sanchez, S., 2011. Dendritic cell maturation and chemotaxis is regulated by TRPM2-mediated lysosomal Ca^{2+} release. FASEB J. 25, 3529–3542.
Sun, X., Chen, W.D., Wang, Y.D., 2015. β-Amyloid: the key peptide in the pathogenesis of Alzheimer's disease. Front. Pharmacol. 6, 221.
Sun, Y., Sukumaran, P., Selvaraj, S., Cilz, N.I., Schaar, A., Lei, S., Singh, B.B., 2018. TRPM2 promotes neurotoxin MPP^{+}/MPTP-induced cell death. Mol. Neurobiol. 55, 409–420.
Sweeney, M.D., Sagare, A.P., Zlokovic, B.V., 2018. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat. Rev. Neurol. 14, 133–150.
Swerdlow, R.H., Burns, J.M., Khan, S.M., 2014. The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. Biochim. Biophys. Acta 1842, 1219–1231.
Syed Mortadza, S.A., Wang, L., Li, D., Jiang, L.H., 2015. TRPM2 channel-mediated ROS-sensitive Ca^{2+} signaling mechanisms in immune cells. Front. Immunol. 6, 407.
Syed Mortadza, S.A., Sim, J.A., Stacey, M., Jiang, L.H., 2017. Signalling mechanisms mediating Zn^{2+}-induced TRPM2 channel activation and cell death in microglial cells. Sci. Rep. 7, 45032.
Syed Mortadza, S.A., Sim, J.A., Neubrand, V.E., Jiang, L.H., 2018. A critical role of TRPM2 channel in Abeta42-induced microglial activation and generation of tumor necrosis factor-alpha. Glia 66, 562–575.
Syntichaki, P., Tavernarakis, N., 2003. The biochemistry of neuronal necrosis: rogue biology? Nat. Rev. Neurosci. 4, 672–684.
Takahashi, N., Kozai, D., Kobayashi, R., Ebert, M., Mori, Y., 2011. Roles of TRPM2 in oxidative stress. Cell Calcium 50, 279–287.
Tamagno, E., Guglielmotto, M., Monteleone, D., Tabaton, M., 2012. Amyloid-β production: major link between oxidative stress and BACE1. Neurotox. Res. 22, 208–219.
Tang, Q., Guo, W., Zheng, L., Wu, J.X., Liu, M., Zhou, X., Zhang, X., Chen, L., 2018. Structure of the receptor-activated human TRPC6 and TRPC3 ion channels. Cell Res. https://doi.org/10.1038/s41422-018-0038-2.
Thibault, O., Gant, J.C., Landfield, P.W., 2007. Expansion of the calcium hypothesis of brain aging and Alzheimer's disease: minding the store. Aging Cell 6, 307–317.
Toledo, J.B., Arnold, S.E., Raible, K., Brettschneider, J., Xie, S.X., Grossman, M., Monsell, S.E., Kukull, W.A., Trojanowski, J.Q., 2013. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. Brain 136, 2697–2706.
Tong, Q., Zhang, W., Conrad, K., Mostoller, K., Cheung, J.Y., Peterson, B.Z., Miller, B.A., 2006. Regulation of the transient receptor potential channel TRPM2 by the Ca^{2+} sensor calmodulin. J. Biol. Chem. 281, 9076–9085.
Tonnies, E., Trushina, E., 2017. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. J. Alzheimer Dis. 57, 1105–1121.
Toth, B., Csanady, L., 2010. Identification of direct and indirect effectors of the transient receptor potential melastatin 2 (TRPM2) cation channel. J. Biol. Chem. 285, 30091–30102.
Toth, B., Iordanov, I., Csanady, L., 2015. Ruling out pyridine dinucleotides as true TRPM2 channel activators reveals novel direct agonist ADP-ribose-2'-phosphate. J. Gen. Physiol. 145, 419–430.
Tschopp, J., Schroder, K., 2010. NLRP3 inflammasome activation: the convergence of multiple signalling pathways on ROS production? Nat. Rev. Immunol. 10, 210–215.
Tsuruda, P.R., Julius, D., Minor Jr, D.L., 2006. Coiled coils direct assembly of a cold-activated TRP channel. Neuron 51, 201–212.
Turlova, E., Feng, Z.P., Sun, H.S., 2018. The role of TRPM2 channels in neurons, glial cells and the blood-brain barrier in cerebral ischemia and hypoxia. Acta Pharmacol. Sin. 39, 713–721.
Uemura, T., Kudoh, J., Noda, S., Kanba, S., Shimizu, N., 2005. Characterization of human and mouse TRPM2 genes: identification of a novel N-terminal truncated protein specifically expressed in human striatum. Biochem. Biophys. Res. Commun. 328, 1232–1243.
van Dyck, C.H., 2018. Anti-amyloid-beta monoclonal antibodies for Alzheimer's disease: pitfalls and promise. Biol. Psychiatry 83, 311–319.
Venkatachalam, K., Montell, C., 2007. TRP channels. Ann. Rev. Biochem. 76, 387–417.
Verma, S., Quillinan, N., Yang, Y.F., Nakayama, S., Cheng, J., Kelley, M.H., Herson, P.S., 2012. TRPM2 channel activation following in vitro ischemia contributes to male hippocampal cell death. Neurosci. Lett. 530, 41–46.
Vinayagam, D., Mager, T., Apelbaum, A., Bothe, A., Merino, F., Hofnagel, O., Gatsogiannis, C., Raunser, S., 2018. Electron cryo-microscopy structure of the canonical TRPC4 ion channel. Elife 7, e36615.
von Bernhardi, R., Tichauer, J.E., Eugenin, J., 2010. Aging-dependent changes of microglial cells and their relevance for neurodegenerative disorders. J. Neurochem. 112, 1099–1114.
Wang, X., Wang, W., Li, L., Perry, G., Lee, H.G., Zhu, X., 2014. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim. Biophys. Acta 1842, 1240–1247.
Wang, J., Jackson, M.F., Xie, Y.F., 2016. Glia and TRPM2 channels in plasticity of central nervous system and Alzheimer's diseases. Neural Plast.(2016), 1680905.
Wehage, E., Eisfeld, J., Heiner, I., Jungling, E., Zitt, C., Luckhoff, A., 2002. Activation of the cation channel long transient receptor potential channel 2 (LTRPC2) by hydrogen peroxide. A splice variant reveals a mode of activation independent of ADP-ribose. J. Biol. Chem. 277, 23150–23156.
Wehrhahn, J., Kraft, R., Harteneck, C., Hauschildt, S., 2010. Transient receptor potential melastatin 2 is required for lipopolysaccharide-induced cytokine production in human monocytes. J. Immunol. 184, 2386–2393.
Wei, L., Syed Mortadza, S.A., Jiang, L.H., 2018. Melastatin-related transient receptor potential 2 channel in Abeta42-induced neuroinflammation: implications to Alzheimer's disease mechanism and development of therapeutics. Neural Regen. Res. 13, 419–420.
Weinstein, J.D., 2018. A new direction for Alzheimer's research. Neural Regen. Res. 13, 190–193.
Wes, P.D., Sayed, F.A., Bard, F., Gan, L., 2016. Targeting microglia for the treatment of Alzheimer's disease. Glia 64, 1710–1732.
White, C.S., Lawrence, C.B., Brough, D., Rivers-Auty, J., 2017. Inflammasomes as therapeutic targets for Alzheimer's disease. Brain Pathol. 27, 223–234.
Wilkins, H.M., Carl, S.M., Greenlief, A.C., Festoff, B.W., Swerdlow, R.H., 2014. Bioenergetic dysfunction and inflammation in Alzheimer's disease: a possible connection. Front. Aging Neurosci. 6, 311.
Winkler, P.A., Huang, Y., Sun, W., Du, J., Lu, W., 2017. Electron cryo-microscopy structure of a human TRPM4 channel. Nature 552, 200–204.
Wolf, S.A., Boddeke, H.W., Kettenmann, H., 2017. Microglia in physiology and disease. Ann. Rev. Physiol. 79, 619–643.
Wyss-Coray, T., Rogers, J., 2012. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. Cold Spring Harb. Perspect. Med. 2, a006346.
Xia, R., Mei, Z.Z., Mao, H.J., Yang, W., Dong, L., Bradley, H., Beech, D.J., Jiang, L.H., 2008. Identification of pore residues engaged in determining divalent cationic permeation in transient receptor potential melastatin subtype channel 2. J. Biol. Chem.

283, 27426–27432.
Xie, Y.F., Belrose, J.C., Lei, G., Tymianski, M., Mori, Y., Macdonald, J.F., Jackson, M.F., 2011. Dependence of NMDA/GSK-3beta mediated metaplasticity on TRPM2 channels at hippocampal CA3-CA1 synapses. Mol. Brain 4, 44.
Xie, H., Guan, J., Borrelli, L.A., Xu, J., Serrano-Pozo, A., Bacskai, B.J., 2013. Mitochondrial alterations near amyloid plaques in an Alzheimer's disease mouse model. J. Neurosci. 33, 17042–17051.
Yamamoto, S., Shimizu, S., 2016. Targeting TRPM2 in ROS-coupled diseases. Pharmaceuticals 9, E57.
Yamamoto, S., Shimizu, S., Kiyonaka, S., Takahashi, N., Wajima, T., Hara, Y., Negoro, T., Hiroi, T., Kiuchi, Y., Okada, T., Kaneko, S., Lange, I., Fleig, A., Penner, R., Nishi, M., Takeshima, H., Mori, Y., 2008. TRPM2-mediated Ca^{2+} influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. Nat. Med. 14, 738–747.
Yamamoto, S., Toda, T., Yonezawa, R., Negoro, T., Shimizu, S., 2017. Tyrphostin AG-related compounds attenuate $_{H2O2}$-induced TRPM2-dependent and -independent cellular responses. J. Pharmacol. Sci. 134, 68–74.
Ye, M., Yang, W., Ainscough, J.F., Hu, X.P., Li, X., Sedo, A., Zhang, X.H., Zhang, X., Chen, Z., Li, X.M., Beech, D.J., Sivaprasadarao, A., Luo, J.H., Jiang, L.H., 2014. TRPM2 channel deficiency prevents delayed cytosolic Zn^{2+} accumulation and CA1 pyramidal neuronal death after transient global ischemia. Cell Death Dis. 5, e1541.
Yin, Y., Wu, M., Zubcevic, L., Borschel, W.F., Lander, G.C., Lee, S.Y., 2018. Structure of the cold- and menthol-sensing ion channel TRPM8. Science 359, 237–241.
Yu, P., Xue, X., Zhang, J., Hu, X., Wu, Y., Jiang, L.H., Jin, H., Luo, J., Zhang, L., Liu, Z., Yang, W., 2017. Identification of the ADPR binding pocket in the NUDT9 homology domain of TRPM2. J. Gen. Physiol. 149, 219–235.
Zekry, D., Epperson, T.K., Krause, K.H., 2003. A role for NOX NADPH oxidases in Alzheimer's disease and other types of dementia? IUBMB life 55, 307–313.
Zhang, W., Chu, X., Tong, Q., Cheung, J.Y., Conrad, K., Masker, K., Miller, B.A., 2003. A novel TRPM2 isoform inhibits calcium influx and susceptibility to cell death. J. Biol. Chem. 278, 16222–16229.
Zhang, Z., Tóth, B., Szollosi, A., Chen, J., Csanády, L., 2018. Structure of a TRPM2 channel in complex with Ca^{2+} explains unique gating regulation. Elife 7, e36409.
Zhong, Z., Zhai, Y., Liang, S., Mori, Y., Han, R., Sutterwala, F.S., Qiao, L., 2013. TRPM2 links oxidative stress to NLRP3 inflammasome activation. Nat. Commun. 4, 1611.
Zlokovic, B.V., 2011. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat. Rev. Neurosci. 12, 723–738.
Zou, J., Ainscough, J.F., Yang, W., Sedo, A., Yu, S.P., Mei, Z.Z., Sivaprasadarao, A., Beech, D.J., Jiang, L.H., 2013. A differential role of macrophage TRPM2 channels in Ca^{2+} signaling and cell death in early responses to H_2O_2. Am. J. Physiol. Cell Physiol. 305, C61–69.
Zubcevic, L., Herzik Jr, M.A., Chung, B.C., Liu, Z., Lander, G.C., Lee, S.Y., 2016. Cryo-electron microscopy structure of the TRPV2 ion channel. Nat. Struct. Mol. Biol. 23, 180–186.
Zundorf, G., Reiser, G., 2011. Calcium dysregulation and homeostasis of neural calcium in the molecular mechanisms of neurodegenerative diseases provide multiple targets for neuroprotection. Antioxid. Redox Signal. 14, 1275–1288.