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MINIREVIEWS

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MINIREVIEWS

Role of STIM1 in neurodegeneration

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Abstract

STIM1 is an endoplasmic reticulum (ER) protein with a key role in Ca^{2+} mobilization. Due to its ability to act as an ER-intraluminal Ca^{2+} sensor, it regulates store-operated Ca^{2+} entry (SOCE), which is a Ca^{2+} influx pathway involved in a wide variety of signalling pathways in eukaryotic cells. Despite its important role in Ca^{2+} transport, current knowledge about the role of STIM1 in neurons is much more limited. Growing evidence supports a role for STIM1 and SOCE in the preservation of dendritic spines required for long-term potentiation and the formation of memory. In this regard, recent studies have demonstrated that the loss of STIM1, which impairs Ca^{2+} mobilization in neurons, risks cell viability and could be the cause of neurodegenerative diseases. The role of STIM1 in neurodegeneration and the molecular basis of cell death triggered by low levels of STIM1 are discussed in this review.

Key words: Alzheimer's disease; Calcium; Neurodegeneration; Parkinson's disease; STIM1; Voltage-operated Ca^{2+} channels

Core tip: STIM1 is an endoplasmic reticulum protein that regulates store-operated Ca^{2+} entry, which is a Ca^{2+} influx pathway involved in a wide variety of signalling pathways. Growing evidence supports a role for this protein, STIM1, in long-term potentiation and the formation of memory. In this regard, the loss of STIM1 observed in brain tissue from Alzheimer's disease patients risks cell viability and could be the cause of neurodegenerative diseases. This is the reason for discussing the role of STIM1 in neurodegeneration in this review.

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STIM1 AND CALCIUM MOBILIZATION

STIM1 (stromal interaction molecule 1) is a type I transmembrane protein located mainly in the endoplasmic reticulum (ER), with a significant pool of approximately 20% at the plasma membrane. Due to its Ca^{2+}-sensitive EF-hand domain close to the N-terminus, STIM1 acts as an ER-intraluminal Ca^{2+} sensor[1,2]. This EF-hand domain shows an apparent dissociation constant for Ca^{2+} of 250 μM[3]. The decrease of the ER-intraluminal Ca^{2+} concentration, with the subsequent dissociation of Ca^{2+} from the EF-hand domain, triggers the oligomerization and the conformational change of STIM1. These two events are critical for STIM1 activation.

The rapid decrease of the ER-intraluminal Ca^{2+} concentration is a common event in cells under diverse stimuli, such as the activation of growth factor receptors or the activation of G protein-coupled receptors. In both cases, phosphoinositide-specific phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate to generate inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol. The generation of IP_3 activates its receptor at the ER, with the subsequent release of Ca^{2+} through this channel/receptor and the rise of cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_c$). As mentioned above, the emptying of intracellular Ca^{2+} stores (mainly the ER) activates STIM1, which is then able to bind and activate STIM1-dependent Ca^{2+} channels[4], such as ORAI1[5]. The activation of ORAI1 leads to the transient increase of Ca^{2+} influx and to the rise of $[Ca^{2+}]_c$, which is required for the refilling of the ER and for the sustainability of this system in successive stimulations. Thus, STIM1 protein and STIM1-dependent Ca^{2+} channels ensure Ca^{2+} mobilization and the stimulation of Ca^{2+}-dependent signaling pathways by activating the "store-operated Ca^{2+} entry" (SOCE), *i.e.*, the Ca^{2+} influx pathway activated by the decrease of the ER-intraluminal Ca^{2+} level.

The activation of plasma membrane Ca^{2+} channels by STIM1 is carried out in ER-plasma membrane contact sites (ER-PM junctions)[6], where STIM1 relocalizes in response to Ca^{2+} store depletion. When the ER-intraluminal Ca^{2+} concentration is high, STIM1 remains bound to the growing tip of microtubules and moves freely on the ER surface[7]. However, activated STIM1 becomes phosphorylated at three ERK1/2-target sites (Ser575, Ser608, and Ser621) and this phosphorylation is critical for enhancing the dissociation from microtubules[8,9]. Oligomers of active STIM1 are less mobile and phospho-STIM1 is found at the cell periphery[10], close to the plasma membrane, where it binds ORAI1. Because STIM1 and ORAI1 are ubiquitous, they are involved in a wide range of signaling pathways that regulate many cellular functions[11]. However, the number of studies about the role of STIM1 in neuronal tissue is much more limited.

STIM1 EXPRESSION AND FUNCTION IN NEURONAL CELLS

STIM1 is widely expressed in the brain according to databases such as Expression Atlas (from the European Bioinformatics Institute, http://www.ebi.ac.uk/gxa) or UniGene (from the National Center for Biotechnology Information, https://www.ncbi.nlm.nih.gov/unigene). Indeed, it is well known that STIM1 becomes activated upon depletion of intracellular Ca^{2+} stores in the brain in a similar fashion to that found in any other cell or tissue[12,13]. The role of STIM1 in neuronal function was initially suggested in *Drosophila melanogaster* neurons. Shortly after the description of STIM1 as the main regulator of SOCE, it was proved that STIM1 was required for normal flight and associated patterns of rhythmic firing of the flight motoneurons[14], and that SOCE regulates spatial and temporal Ca^{2+} mobilization in vertebrate photoreceptor cones, suggesting a role in the generation of excitatory signals across the retinal synapse[15].

A key finding was reported in 2010 by Ricardo Dolmetsch's and Donald L. Gill's labs. They found that STIM1 directly suppresses depolarization-induced opening of the voltage-operated Ca^{2+} channel (VOCC) $Ca_V1.2$[16,17]. What was striking was the fact that STIM1 binds to $Ca_V1.2$ through the same domain that activates ORAI1, the Ca^{2+} release-activated Ca^{2+} activation domain, and also triggers the internalization of the channel from the membrane. These findings provided the molecular explanation for the shared control of Ca^{2+} entry through ORAI1 and $Ca_V1.2$, making it possible for them to operate independently. In HEK293 cells, it was later reported that Homer proteins are required for the binding between STIM1 and $Ca_V1.2$ channels upon Ca^{2+} store-depletion conditions triggered by thapsigargin[18], an inhibitor of the ER-Ca^{2+} pump.

T-type VOCCs, such as $Ca_V3.1$, are also modulated by STIM1. This was first observed not in neurons but in cardiomyocytes, where it was reported that STIM1 co-precipitated with $Ca_V1.3$ channels, and that the knocking-down of STIM1 expression

increased $Ca_V1.3$ surface expression and the current density of T-type VOCCs[19].

Given the abundance of STIM1 and STIM2 in neuronal tissues and their role in Ca^{2+} mobilization, it is not surprising to learn that they have a direct impact on cognitive functions. In mice with conditional deletion of Stim1 or Stim2 genes in the forebrain (conditional knock-outs or cKO), the analysis of spatial reference memory revealed a mild learning delay in Stim1 cKO mice, no effect in Stim2 cKO mice, and a deep impairment in spatial learning in the double cKO[20]. This striking effect was explained by the regulation of the phosphorylation of the AMPA receptor subunit GluA1, the transcriptional regulator CREB and the $Ca_V1.2$ on protein kinase A-target sites, leading to the proposal that the upregulation of cAMP/PKA signaling impairs the development of spatial memory[20]. Kuznicki's lab reported that STIM1 protein in neurons can control AMPA-induced Ca^{2+} entry, based on the inhibition of Ca^{2+} entry observed with AMPA receptors (AMPAR) inhibitors and the finding that STIM1 physically binds GluA1/GluA2 AMPAR[21].

On the other hand, in transgenic mice overexpressing STIM1 in neurons it was reported a reduction of long-term depression in hippocampal slices, as well as a decrease in anxiety-like behavior and an increase in contextual learning improvement[22]. All of this further confirms the role of STIM1 in the modulation of synaptic strength and memory formation.

Closely related to the above statement, the control of L-type VOCCs by STIM1 has functional consequences that were reported for dendritic spine structural plasticity. In hippocampal neurons, depolarization by the neurotransmitter glutamate activates postsynaptic N-methyl-D-aspartate receptors and L-type VOCC-dependent Ca^{2+} influx, as well as the release of Ca^{2+} from the ER. The consequent activation of STIM1 inhibits VOCCs, an event that leads to the enlargement of ER content in spines, which is believed to help in the stabilization of mushroom spines that have become enlarged during long-term potentiation[23].

STIM1 IN NEURONAL CELL DEATH

There are some examples of the involvement of STIM1 and SOCE in neuronal injury. For instance, cell death due to diffuse axonal injury is preceded by an increase of STIM1 expression in neurons of the rat cerebral cortex after lateral head rotational injury[24]. In this regard, STIM1 expression was significantly increased in a traumatic brain injury model, and STIM1 knock-down inhibited apoptotic cell death after traumatic injury by decreasing the upregulation of mGluR1-dependent Ca^{2+} signaling[25]. However, Berna-Erro *et al*[26] demonstrated that STIM2, but not STIM1, was essential for ischemia-induced cytosolic Ca^{2+} accumulation in neurons using hypoxic conditions for culturing neurons from wild-type and $Stim2^{-/-}$ mice, hippocampal slice preparations, as well as in $Stim2^{-/-}$ mic subjected to focal cerebral ischemia.

Oxytosis, a type of cell death characterized by an increase of reactive oxygen species (ROS) and augmented Ca^{2+} influx, can be triggered in neurons in culture by depleting reduced glutathione content. Henke *et al*[27], reported that the Ca^{2+}-influx pathway in this cell death could be mediated by ORAI1, the CRAC channel activated by STIM1. Similarly, in PC12 cells exposed to 6-hydroxydopamine (6-OHDA), an experimental model to trigger ROS-dependent cell death, the knockdown of STIM1 was able to attenuate apoptotic cell death by limiting the mitochondrial Ca^{2+} uptake induced by 6-OHDA. This resulted in the protection of PC12 cells against the oxidative stress generated by ER stress and mitochondrial dysfunction[28]. On the other hand, the inhibition of SOCE or the knock-down of STIM1 limited ROS production and the activation of apoptosis in PC12 cells exposed to 1-methyl-4-phenylpyridinium or MPP^+[29], the toxic metabolite of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a well-known inducer of Parkinsonism. These studies revealed that oxidative stress induces an increase of $[Ca^{2+}]_i$ mediated by the activation of SOCE. Indeed, STIM1 is a redox-sensitive protein, and it is known that Cys56 becomes S-glutathionylated during oxidative stress[30], a residue located near its luminal EF-hand domain. Hawkins *et al*[30], demonstrated that S-glutathionylation lowered the affinity of STIM1 for Ca^{2+}, thereby activating STIM1 in a store-independent fashion. Similarly, ORAI1 is a redox sensor through the Cys195 located in the second extracellular loop. Although it was initially shown that the oxidation of this Cys residue inhibited Ca^{2+} current through this channel[31], other researchers found that exposure to H_2O_2 increased influx through ORAI1[32], suggesting that ROS has multiple redox-sensitive targets in the SOCE machinery.

Mitochondrial dysfunction is an early event in neurotoxicity triggered by massive Ca^{2+} influx, as observed during glutamate neurotoxicity[33]. Following acute increase in

$[Ca^{2+}]_i$, Ca^{2+} uptake by mitochondria contributes to the protection against cell death. However, Ca^{2+} overload in mitochondria triggers the opening of the mitochondrial permeability transition pore (mPTP), an event that led to cell death in different neuronal cell types[34,35]. It is accepted that the overproduction of ROS modulates the opening of the mPTP, but it has also been shown this opening at physiological levels of ROS. Recently, Agarwal *et al*[36], reported that astrocytes show transient cytosolic Ca^{2+} spikes generated by the Ca^{2+} release from mitochondria when the mPTP opens by a mechanism that involves ROS generated during the electron transfer in the respiratory systems. Electron transport rates are strongly dependent on the availability of NADH, and therefore dependent on the Krebs cycle status, which is tightly controlled by the mitochondrial $[Ca^{2+}]$. Therefore, there is a strong correlation between dysregulation of Ca^{2+} entry through ORAI1, mitochondrial Ca^{2+} overload, ROS generation, mPTP opening and cell death.

STIM1 IN NEURODEGENERATIVE DISEASES

Alzheimer's disease

Taking into consideration the information summarized above, it should not be surprising that the dysregulation of STIM1 could underlie the pathogenesis of some of the most frequent neurodegenerative diseases. In 1907 Alzheimer[37] described a disease in a 51-year-old woman with presenile dementia who displayed diffuse cortical atrophy, nerve cell loss, plaques, and tangles. Nowadays, Alzheimer's disease (AD) patients are classified within 3 groups: Early-onset AD (up to 5% of all patients with AD), late-onset or sporadic AD (the most common form of the disease), and familial AD (FAD, less than 1% of AD patients). FAD is linked to known genes, such as the amyloid beta precursor protein gene (*APP*), the apolipoprotein E gene (*APOE*), presenilin1/2 genes (*PSEN1, PSEN2*), or the alpha-2-macroglobulin gene (*A2M*), and most early–onset AD patients are FAD patients. There is no significant pathological dierence between sporadic AD and FAD, but symptoms progress more rapidly in FAD[38].

The major risk for sporadic AD is aging, which increases the difficulty of finding a suitable model animal that recapitulates all the hallmarks of the human disease in the absence of mutated genes as in FAD. However, there is a growing consensus regarding the hypothesis that Ca^{2+} dysregulation is in the pathogenesis of AD[39-42]. This hypothesis is supported by evidence that revealed how diverse Ca^{2+} mobilization systems are impaired in AD, including VOCCs, IP_3 receptors, store-operated Ca^{2+} channels (SOCs), and mitochondrial Ca^{2+} transporters[43].

Regarding STIM1 and SOCE, it is known that SOCE is reduced and that STIM1 and ORAI1 expression are downregulated in long-term cultures of hippocampal neurons, an experimental approach intended to mimic in vivo neuronal aging[44]. Also, reduced expression of STIM2 was observed in hippocampal neurons from the presenilin-1 M146V knock-in mouse model of FAD. As it is assumed that STIM2 and the activation of the calmodulin-dependent protein kinase II (CaMKII) mediates the stabilization of mushroom spines, this decrease in STIM2 levels could explain the loss of dendritic spines and the defects in the development of long-term potentiation LTP and memory development in AD patients[45]. In this regard, it is known that the gamma-secretase protein complex interacts with STIM1 in SH-SY5Y neuroblastoma cells, skin fibroblasts from FAD patients, and in mouse primary cortical neurons[46]. Tong *et al*[46], also reported that cultured hippocampal neurons expressing the mutant PSEN1 M146L, showed reduced dendritic spines, together with diminished SOCE. Because the wild-type phenotype was rescued by overexpressing STIM1, or by inhibiting gamma-secretase activity, they hypothesized that STIM1 could be a substrate for the gamma-secretase complex. Finally, they proved that the transmembrane domain of STIM1 shows a target domain for the proteolytic activity of the gamma-secretase complex and that the reduced SOCE in PSEN1-mutant neurons was due to the higher rates of STIM1 proteolysis. Although this proteolysis needs to be studied further to confirm cleavage sites on STIM1, this data fits well with the recent observation that there is a sharp decline of STIM1 protein levels in brain tissue from non-familial (sporadic) AD patients[47]. This is supporting evidence for a common hallmark in sporadic AD and FAD, *i.e.*, reduced STIM1 could be severely affecting Ca^{2+} mobilization in neurons in both groups of patients. Thus, it is necessary to study the consequences of the reduced STIM1 expression in neurons in order to understand how neuronal cell physiology develops in the absence of STIM1 and to find possible targets for clinical interventions. An approach to studying the patho-physiological consequences of a limited level of STIM1 in neurons has been recently reported by our group[47]. In this report, we modified *STIM1* gene locus using CRISPR/Cas9-mediated

editing techniques, and we found that the differentiation of SH-SY5Y cells to neuronal-like cells was not impaired by the absence of STIM1. However, the loss of STIM1 triggered significant cell death due to the impairment of mitochondrial respiratory chain complex I, and to reduced mitochondrial Ca^{2+} concentration. These two events led to high levels of senescence. STIM1-KO cells showed potentiation of Ca^{2+} entry through L-type VOCCs[47], further confirming earlier observations that demonstrated the inhibitory role of STIM1 on $Ca_V1.2$ channels[16,17]. Consequently, the knocking-down of *CACNA1C* gene transcripts (for $Ca_V1.2$ channel) rescued the wild-type phenotype, confirming that the upregulation of Ca^{2+} entry through $Ca_V1.2$ channels was deleterious in STIM1-deficient cells[47] (Figure 1). In this regard, higher Ca^{2+} entry through VOCCs had been recorded in CA1 pyramidal neurons from the hippocampus in aged rats[48], an effect that resulted in the down-regulation of short-term neuronal plasticity.

Accumulation of beta amyloid peptides (APP) begins earlier than most of the clinical symptoms associated with FAD. However, clinical interventions to prevent this accumulation have been inconclusive so far. Accumulation of APP directly affects Ca^{2+} mobilization, and the possibility that an increase of PKA-dependent phosphorylation of $Ca_V1.2$ channels could underlie the upregulation of Ca^{2+} influx through these channels has been discussed[49,50]. Therefore, an alternative clinical intervention is the blocking of excessive Ca^{2+} entry in neurons. Transgenic mice have been designed to accumulate APP and hyperphosphorylation of tau protein in CA1 pyramidal neurons, as an experimental approach to mimic some clinical features of FAD patients. Using these mice (known as 3xTgAD mice) it has been shown that Ca^{2+} current through L-type VOCCs became higher in these hippocampal neurons, supporting the possible role of VOCCs in neuronal degeneration in FAD patients[51]. In addition, the long-term treatment of subjects receiving active treatment with L-type VOCCs blockers (nitrendipine) reduced sporadic dementia by 55% during aging[52], suggesting that the enhanced Ca^{2+} entry through VOCCs could be in the pathogenesis of sporadic AD. Protection against the loss of working memory has also been monitored in rats treated with the VOCC blocker nimodipine, a treatment that reduced Ca^{2+} current through $Ca_V1.3$ in CA1 neurons[53]. Finally, isradipine, another dihydropyridine, attenuated APP accumulation toxicity by reducing $Ca_V1.2$ expression and Ca^{2+} influx in MC65 neuroblastoma cells[54]. Interestingly, isradipine also showed a neuroprotective effect in models of Parkinson's disease (PD) and stroke[50,55].

Whereas a decline in STIM1 level is deleterious, in part due to the upregulation of VOCCs, high levels of STIM1 and SOCE might be protective, as suggested by the reduced APP secretion observed in cells expressing a constitutively activated STIM1 mutant (D76A)[56]. On the other hand, APP seems to affect STIM1-dependent Ca^{2+} entry because knocking-down APP transcripts delayed the binding of STIM1 to ORAI1 in response to store depletion[57], and SOCE was largely reduced in cultured astrocytes from APP-KO mice[58], confirming the crosstalk between SOCE and APP.

PD

A recent report showed that neurotoxins that trigger PD symptoms targeted TRPC1 expression and increased Ca^{2+} influx through $Ca_V1.3$ channels (L-type VOCC) which led to degeneration of dopaminergic (DA) neurons[59]. Because of the key role of $Ca_V1.3$ in the regulation of basal single-spike firing in DA neurons[60], the reported inhibition of $Ca_V1.3$ by the STIM1-TRPC1 complex[59] could explain the disruption of neuronal Ca^{2+} homeostasis in PD patients. Indeed, in mice treated with MPTP, the expression of $Ca_V1.2$ and $Ca_V1.3$ in the substantia nigra increased after 2 wk of treatment, and isradipine (L-type VOCC blocker) prevented this upregulation and the loss of DA neurons[61]. Similarly, nimodipine prevented cell death triggered by MPP^+ in SH-SY5Y cell in culture and Parkinsonism in MPTP-treated mice[62]. Because dihydropyridines are not highly selective in discriminating between $Ca_V1.2$ and $Ca_V1.3$, Wang *et al*[61], reported a high-throughput screening that led to 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione as the first potent and highly selective $Ca_V1.3$ antagonist with potential utility in clinical approaches. However, Ortner *et al*[63], reported later that this specific compound showed inhibitory activity of $Ca_V1.3$ only in a minority of cells.

On the other hand, antagonists of SOCE and depletion of STIM1 by siRNA increased cell viability, reduced intracellular ROS production as well as lipid peroxidation and prevented mitochondrial dysfunction in MPP^+-treated PC12 cells[29], supporting the hypothesis that augmented Ca^{2+} entry through STIM1-activated channels mediates toxicity of MPP^+. This result, however, is in conflict with the

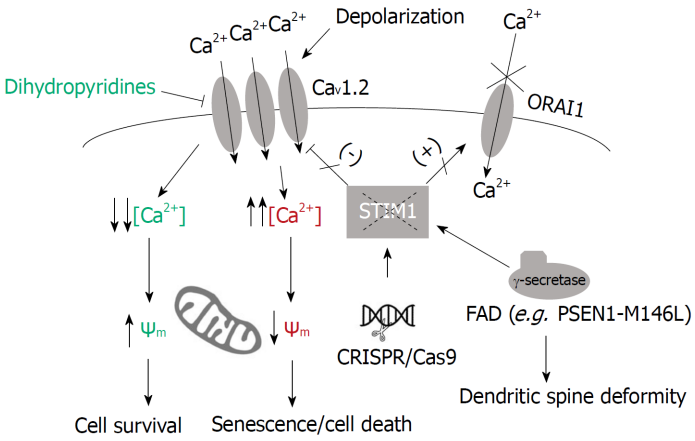

Figure 1 Deficiency of STIM1 and neurodegeneration. Neurons expressing the mutant PSEN1 M146L showed higher rates of STIM1 proteolysis, reduced levels of STIM1, reduced store-operated Ca^{2+} entry and diminished dendritic spines[46]. Deficiency of STIM1 has been observed in non-familial (sporadic) Alzheimer's disease (AD) patients, and can be mimicked by genome edition of STIM1 locus in SH-SY5Y cells[47]. Because STIM1 is a negative regulator of $Ca_V1.2$ channels, this deficiency triggered the upregulation of Ca^{2+} entry through $Ca_V1.2$ channels which was responsible for the loss of inner mitochondrial membrane polarization, senescence, and cell death[47]. This higher rate of Ca^{2+} influx through $Ca_V1.2$ channels has also been monitored in 3xTgAD mice[51]. The long-term treatment with dihydropyridines, known blockers of $Ca_V1.2$, reduced sporadic dementia by 55% during aging[52], pointing out the decrease of STIM1 as a possible mechanism to explain neurodegeneration in sporadic and familial AD.

observation that treatment with this neurotoxin decreased TRPC1 expression, TRPC1 interaction with STIM1, and Ca^{2+} entry in SH-SY5Y cells[64], making further study necessary to discover the role of STIM1, SOCE, and VOCCs in the pathogenesis of PD.

CONCLUSION

Neurodegenerative diseases are devastating for the elderly population and no fully efficient therapies are available to treat some of them, particularly AD. However, a growing body of evidence supports a role for excessive Ca^{2+} entry through VOCCs in neurodegeneration. Recent reports proposed that the specific loss of STIM1 in neuronal tissue fully explains the observed Ca^{2+} homeostasis disruption in neurons during sporadic AD and FAD. In this regard, STIM1 deficiency triggered upregulation of Ca^{2+} entry through $Ca_V1.2$ in differentiated SH-SY5Y cells, which can be explained by the role of STIM1 in the inhibitory control of $Ca_V1.2$. This augmented Ca^{2+} influx led to the inhibition of the mitochondrial respiratory chain complex I activity, mitochondrial inner membrane depolarization, reduced mitochondrial free Ca^{2+} concentration, and to higher levels of senescence and cell death. All these effects were prevented by silencing $Ca_V1.2$ expression, emphasizing the upregulation of these channels as a major cause of neuronal cell death (Figure 1).

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