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REVIEW ARTICLE

Calcium Signaling, PKC Gamma, IP_3R1 and CAR8 Link Spinocerebellar Ataxias and Purkinje Cell Dendritic Development

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Abstract: ***Background*:** Spinocerebellar ataxias (SCAs) are a group of cerebellar diseases characterized by progressive ataxia and cerebellar atrophy. Several forms of SCAs are caused by missense mutations or deletions in genes related to calcium signaling in Purkinje cells. Among them, spinocerebellar ataxia type 14 (SCA14) is caused by missense mutations in PRKCG gene which encodes protein kinase C gamma (PKCγ). It is remarkable that in several cases in which SCA is caused by point mutations in an individual gene, the affected genes are involved in the PKCγ signaling pathway and calcium signaling which is not only crucial for proper Purkinje cell function but is also involved in the control of Purkinje cell dendritic development. In this review, we will focus on the PKCγ signaling related genes and calcium signaling related genes then discuss their role for both Purkinje cell dendritic development and cerebellar ataxia.

***Methods*:** Research related to SCAs and Purkinje cell dendritic development is reviewed.

***Results*:** PKCγ dysregulation causes abnormal Purkinje cell dendritic development and SCA14. Carbonic anhydrase related protein 8 (*Car8*) encoding CAR8 and *Itpr1* encoding IP3R1were identified as upregulated genes in one of SCA14 mouse model. IP3R1, CAR8 and PKCγ proteins are strongly and specifically expressed in Purkinje cells. The common function among them is that they are involved in the regulation of calcium homeostasis in Purkinje cells and their dysfunction causes ataxia in mouse and human. Furthermore, disruption of intracellular calcium homeostasis caused by mutations in some calcium channels in Purkinje cells links to abnormal Purkinje cell dendritic development and the pathogenesis of several SCAs.

***Conclusion*:** Once PKCγ signaling related genes and calcium signaling related genes are disturbed, the normal dendritic development of Purkinje cells is impaired as well as the integration of signals from other neurons, resulting in abnormal development, cerebellar dysfunction and eventually Purkinje cell loss.

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1. INTRODUCTION

Cerebellar Purkinje cells are among the best known neurons in the brain due to their large and elaborated dendritic trees [1]. They are the principal output neurons of the cerebellar cortex, therefore Purkinje cell dysfunction results in multiple cerebellar diseases. Purkinje cell survival and function are compromised in spinocerebellar ataxias (SCAs). This is a group of hereditary neurodegenerative diseases with impaired function of the spinocerebellum [2]. Although there are sporadic forms of SCAs, the term is most often used to refer to the hereditary forms [3, 4]. In hereditary SCA, cerebellar neurons or non-neuronal cells (*e.g*. Bergmann glial cells) can be affected by the gene defect [5, 6]. Currently, 42 SCA types are known (the number is continuously increasing). The clinical aspect of SCAs is heterogeneous with various symptoms, characterized by a slowly progressive incoordination of gait often associated with poor limb coordination, dysarthria and cerebellar oculomotor disorders [5]. The most common forms of SCAs are caused by expansion of CAG repeats in members of the ataxin gene family [7]. In contrast,

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several other forms of SCAs are caused by single missense mutations or deletions in genes which encoding proteins often related to the calcium signaling cascade in Purkinje cells. Examples for targets of such missense mutations are protein kinase C gamma (PKCγ) causing SCA14 [8] and the inositol 1, 4, 5-trisphosphate receptors type 1 (IP_3R1) causing SCA15/16 [9-11] and SCA29 [12]. Moreover, also some CAG mutations may affect calcium signaling in Purkinje cells [13, 14].

It is remarkable that in several cases in which SCA is caused by point mutations in an individual gene, the affected genes are involved in the PKCγ signaling pathway and calcium signaling which is not only crucial for proper Purkinje cell function but is also involved in the control of Purkinje cell dendritic development [15].

Furthermore, PKCγ signaling pathway related proteins in Purkinje cells such as transient receptor potential cation channel type 3 (TRPC3) and metabotropic glutamate receptor type 1 (mGluR1) have influence on Purkinje dendritic development and mutations in these genes cause cerebellar ataxia in mice or humans [16, 17]. In this article, we will focus on the role of the affected calcium signaling molecules both for Purkinje cell dendritic development and for spinocerebellar ataxia.

2. Ca^{2+} HOMEOSTASIS IN PURKINJE CELL DENDRITIC DEVELOPMENT AND ATAXIA

Disruption of intracellular calcium (Ca^{2+}) homeostasis in Purkinje cells is thought to be a key mechanism in the pathogenesis of SCA and at the same time is known to control Purkinje cell dendritic development. Chronic activation of mGluR1 induces a pronounced reduction of the size and branching of the Purkinje cell dendritic tree [18]. This inhibition of Purkinje cell dendritic development after chronic activation of mGluR1 is partially rescued by inhibition of T-type and P/Q-type calcium channels [16], indicating that Ca^{2+} influx through T-type and P/Q-type channels is important for mGluR1 mediated dendritic growth inhibition.

SCA6 is caused by CAG expansions in the *CACNA1A* gene [19] which codes for the P/Q-type calcium channel Cav2.1. Although SCA6 is a polyglutamine disease, the polyglutamine stretch was shown to change the channel properties of Cav2.1 [20] causing a dysfunction of this channel [13, 14]. However, the pathogenic significance of this effect for the development of the SCA phenotype is still open [13]. The *tottering* mouse has a mutation in Cav2.1 [21], which results in reduced Ca^{2+} currents in cerebellar Purkinje cells. These mice have cerebellar ataxia and show intermittent absence seizures, which indicate the important role of Cav2.1 function in Purkinje cells [22]. In agreement with the important role of P/Q-type calcium channels, the dendritic arbor of the Purkinje cells in the *tottering* mouse is reduced in size and complexity [23].

The importance of the Ca^{2+} homeostasis for Purkinje cell dendritic development is further demonstrated by *lurcher* mutant mice which have increased calcium entry *via* a mutated GluR-delta2 channel resulting in a much reduced dendritic development which can be rescued by blocking Ca^{2+} influx through this channel [24]. Interference with Ca^{2+} clearance mechanisms also affects Purkinje cell dendritic development. Inhibition of the plasma membrane Ca^{2+}-ATPase2 (PMCA2) activity by carboxyeosin resulted in a reduction of Purkinje cell dendritic growth [25]. Interestingly, it is known that PMCA2 does co-immunoprecipitate with mGluR1, Homer3 and IP_3R1, which suggests that the Ca^{2+} pump PMCA2, mGluR1, Homer3 and the IP_3R1 might be forming a complex and regulate each other [26].

Another mutation affecting the Ca^{2+} homeostasis in Purkinje cells is found in *Moonwalker* (*Mwk*) mice which have a point mutation in the TRPC3 leading to increased calcium influx. *Mwk* mice develop cerebellar ataxia [17] and also have abnormal dendritic arborization during cerebellar development [27]. Recently, mutations in the *TRPC3* gene were linked to spinocerebellar ataxia in humans [28] and have been classified as SCA41. Interestingly, *Trpc3* knockout mice showed normal dendritic development [16], indicating that an increased Ca^{2+} entry through the TRPC3 channel and not a loss of function did cause abnormal dendritic development and ataxia in the *Mwk* mice. Another report showed that CHO cells transfected with PKCγ carrying the G118D-PKCγ mutation showed increased Ca^{2+} entry through TRPC3 channels due to decreased phosphorylation of this channel by the mutant PKCγ [29]. This raises the possibility that PKCγ might be mediating Ca^{2+} entry through TRPC3 channels also in Purkinje cells. Dulneva *et al*. showed that CaMKIV is hyper-phosphorylated in the *Mwk* cerebellum and might be one candidate for the downstream signaling of the TRPC3 mediated Ca^{2+} overload [30]. One of the downstream targets of CaMKIV is retinoid-related orphan receptor α (RORα) which is a key factor for early dendritic development of Purkinje cells [30, 31].

3. PKCγ AND SCA14

By now, almost 40 different mutations or deletions in the *PRKCG* gene which encodes PKCγ are known to cause SCA14, but it is still unclear how these mutations ultimately cause Purkinje cell dysfunction and death as seen in SCA14. Remarkably, PKCγ-deficient mice only show mild ataxia and no gross morphological abnormalities in the cerebellum [8, 32]. Furthermore, SCA14 is a dominantly inherited disease indicating that a toxic gain of function or a dominant negative function rather than a loss of function of PKCγ causes SCA14. There are several reports about the kinase activity of mutant PKCγ found in SCA14. An early report showed that two SCA14 missense mutations were functionally increasing PKCγ catalytic activity, linking Purkinje cell degeneration to a potential gain of function phenotype of PKCγ [33]. Another report showed that 19 out of the 20 tested PKCγ mutations showed an increased constitutive activity of PKCγ and increased Ca^{2+} levels in the cytoplasm in a cell based assay, which suggests that a gain of function of PKCγ could underlie the pathology of SCA14 [29]. On the other hand, there is evidence that in particular SCA14 mutations in C1 domain might be functionally defective due to decreased binding to Diacylglycerol (DAG) [34]. These controversial findings suggest that it may not be the increase or decrease of PKCγ activity as such but rather the loss of the ability of the Purkinje cell to rapidly adapt the activity of

PKCγ to the changing requirements of different functional states which eventually will result in a long-lasting dysfunction and the development of the ataxic phenotype.

It was also reported that mutant PKCγ protein aggregates in the cytoplasm of cultured cells transfected with PKCγ mutations [35, 36]. When mutant PKCγ transfected cells were treated by rapamycin, an inducer of autophagy, cells demonstrated an accelerated clearance of aggregates, indicating that autophagy can contribute to the degradation of mutant PKCγ [37]. However, in primary cultures of Purkinje cells transfected with PKCγ mutations, abnormal dendritic development of Purkinje cells also occurred independent of aggregate formation [38] therefore the role of these aggregates in the pathogenesis of SCA14 is still not clear. There is another report that amyloid-like oligomers and fibril formation of mutant PKCγ may contribute to SCA14 pathogenesis [39]. In this report SCA14 related C1 domain mutations promoted the amyloid-like fibril formation of PKCγ both in cells and *in vitro*. Although endogenous PKCγ itself may form amyloid-like fibrils, SCA14 related mutations accelerated this process substantially. PKCγ protein amyloid-like fibril formation thus might also contribute to SCA14 pathogenesis. However, direct proof that amyloid or aggregate formation is involved in Purkinje cell death in SCA14 is still missing.

Several groups have been searching for proteins interacting with mutant PKCγ and being potentially involved in the pathogenesis of SCA14. However, it has been found that many known PKCγ substrate proteins are not directly associated with SCA14 or Purkinje cell degeneration, such as metabotropic glutamate receptor 5 (mGluR5), non-muscle myosin heavy chain II-B, myristoylated alanine-rich C-kinase substrate (MARCKS) and GAP43/B-50 [40]. Aprataxin (APTX), which is a DNA repair protein and associated with autosomal recessive ataxia with oculomotor apraxia type 1 (AOA1) [41], was shown to be a candidate substrate of SCA14 mutant PKCγ [40].

Most of these studies used *in vitro* assays based on cell lines like CHO or COS7 cells in order to search for pathogenic mechanisms of SCA14 and produced conflicting results (see above). In order to clarify the molecular mechanisms leading to SCA14 in Purkinje cells a detailed analysis of the effects of mutant PKCγ within Purkinje cells is required. Shuvaev *et al*. reported that after lentiviral transfection of the C1 domain mutant PKCγ, aggregated PKCγ formation and impaired LTD in transfected Purkinje cells were observed, but there was no signs of Purkinje cell degeneration within the three weeks of transfection [42]. There are also reports of transgenic mouse models of SCA14. In a mouse model with ubiquitous expression of a human mutant PKCγ carrying the C1 domain mutation H101Y, a loss of Purkinje cells at the age of four weeks and stereotypic clasping responses in the hind limbs were reported [43]. Previous work had suggested that this mutation had a dominant negative effect on endogenous wild type PKCγ enzyme activity leading to uncontrolled, open gap junctions in cells expressing the H101Y-PKCγ mutation [43, 44]. Since the original short report about this mouse model in 2009, no further studies have been published. Ji *et al*. introduced a transgenic mouse model in which PKCγ with the kinase domain mutation S361G was specifically expressed in Purkinje cells using the L7 promoter [45]. S361G-PKCγ transgenic mice showed a mild ataxic phenotype and abnormal Purkinje cell dendritic morphology in organotypic slice culture strongly indicative of a high constitutive PKC activity [45]. The S361G-PKCγ transgenic mice offered the possibility to search for genes specifically regulated in Purkinje cells with an increased PKCγ activity because of the presence transgene. Using this approach carbonic anhydrase related protein 8 (*Car8*) and *Itpr1* were identified as upregulated genes in S361G transgenic mice [46].

4. IP$_3$R1 AND SCA15/16 & SCA29

IP$_3$Rs are membrane glycoproteins activated by inositol trisphosphate (IP3) and IP$_3$Rs function as a ligand-gated ion channel that releases Ca^{2+} from intracellular stores [47]. There are three isoforms of IP$_3$Rs, called types 1 (IP$_3$R1), 2 (IP$_3$R2), and 3 (IP$_3$R3). In many mammalian cells more than one of these isoforms are expressed, often all three isoforms [48]. IP$_3$R1 is the major neuronal IP$_3$R isoform in the central nervous system and it is abundant in the cerebellum, predominantly in Purkinje cells [49]. It has been suggested to be one of the key proteins in the pathogenesis of SCAs [50]. *Itpr1* knock-out mice have a severe ataxia [10, 51] and Purkinje cells from these mice show abnormal dendritic development in dissociated cultures [52, 53]. In humans, two SCA subtypes are associated with the *ITPR1* gene: SCA15/16 is caused by deletions or missense mutations in the *ITPR1* gene [9, 11, 54] and SCA29 is caused by missense mutations in *ITPR1* [55]. SCA29 is distinguished from SCA15/16 by clinical characteristics like early onset and delayed motor development [12, 55] but SCA15/16 and SCA29 reflect the same genetic target. Both forms show a dominant inheritance and it is not yet clear whether the disease is caused by a lack of sufficient functional IP$_3$R1 protein or whether there also might be a toxic gain of function involved [56]. In heterozygous IP$_3$R1-deficient mice there was no major phenotype found besides a mild motor discoordination [57]. It has been reported that one SCA15 mutation still has a functional Ca^{2+} release channel [58] and no other neuropathological mechanisms in SCA15/16 have been proposed to date [50]. In SCA29, at least six different point mutations have been identified [55]. One of these mutations is located in the CAR8 binding region [59] which might change IP3 binding affinity to the IP$_3$R1. In a recent study, it was shown that "Gillespie syndrome", a rare hereditary disease with iris malformation and cerebellar ataxia, is also caused by point mutations in the *ITPR1* gene which are thought to have a dominant negative action [60, 61].

Interestingly, ataxin-2 and ataxin-3 which are the mutated proteins in SCA2 and SCA3 respectively have been shown to interact with the IP$_3$R1, probably by increasing Ca^{2+} release to the cytoplasm [62]. If IP$_3$R1-mediated Ca^{2+} signaling is blocked by overexpression of the IP3R1 suppressor inositol 1, 4, 5-phosphatase (Inpp5a) or by stabilizing intracellular calcium levels with the drug dantrolene [62], Purkinje cell death by dark cell degeneration in SCA2 and SCA3 mouse models could be reduced [63, 64]. These findings indicate that IP$_3$R1 mediated Ca^{2+} signaling is also a key

mechanism in pathogenesis of SCA2 and SCA3 [50]. It is intriguing that while in SCA15 and SCA29 there is evidence that the cerebellar phenotype is caused by a loss of function of the IP_3R1 either through dominant negative effects or through haploinsufficiency, it seems to be converse in SCA2 and SCA3 where a gain of function of the IP_3R1 is assumed through binding of the mutated ataxin proteins [65]. These opposing results suggest that it may not be the reduced or increased activity of the IP_3R1 as such but rather the loss of a precise regulation of its activity that causes the disease. In such a scenario it does not matter to which side the functional IP_3R1 activity is shifted but it would be the loss of regulation that eventually compromises Purkinje cell function and survival [66].

5. CAR8 AND ATAXIA

CAR8 is a member of the carbonic anhydrase family which lacks enzymatic activity. It is predominantly expressed in the central nervous system, in particular there is a strong expression in cerebellar Purkinje cells [59, 67, 68]. In zebrafish, *Car8* knockdown resulted in abnormal cerebellar development and ataxia [69]. In human patients, mutations in the *CA8* gene were identified which are associated with cerebellar ataxia and mild cognitive retardation [70, 71]. Autoantibodies directed against CAR8 have been identified as a cause of Purkinje cell degeneration and cerebellar ataxia in paraneoplastic syndromes [72]. Mice carrying a 19-base-pair deletion in the *Car8* gene have no CAR8 protein expression and the loss of function of CAR8 in these *waddles* (*wdl*) mouse mutants [67] results in ataxia accompanied by synaptic changes in the cerebellum which are associated with alterations in calcium regulation [73]. Interestingly, this marked ataxic syndrome occurs in the absence of gross anatomical defects and loss of Purkinje cells. Only a certain developmental delay was observed during early cerebellar development in *wdl* mice [67, 74]. In contrast, the zonal architecture of the cerebellar cortex was changed and abnormal Purkinje cell firing *in vivo* was observed [74]. This phenotype has similarities to that of mice with a Purkinje cell specific inactivation of the Cav2.1 Ca^{2+} channels [75]. These findings indicate that Ca^{2+} dysregulation through CAR8 or Cav2.1 can cause ataxia in the absence of Purkinje cell loss. Both *Car8* and *Itpr1* mRNAs were found to be downregulated in the *staggerer* mouse and in a SCA1 mouse model

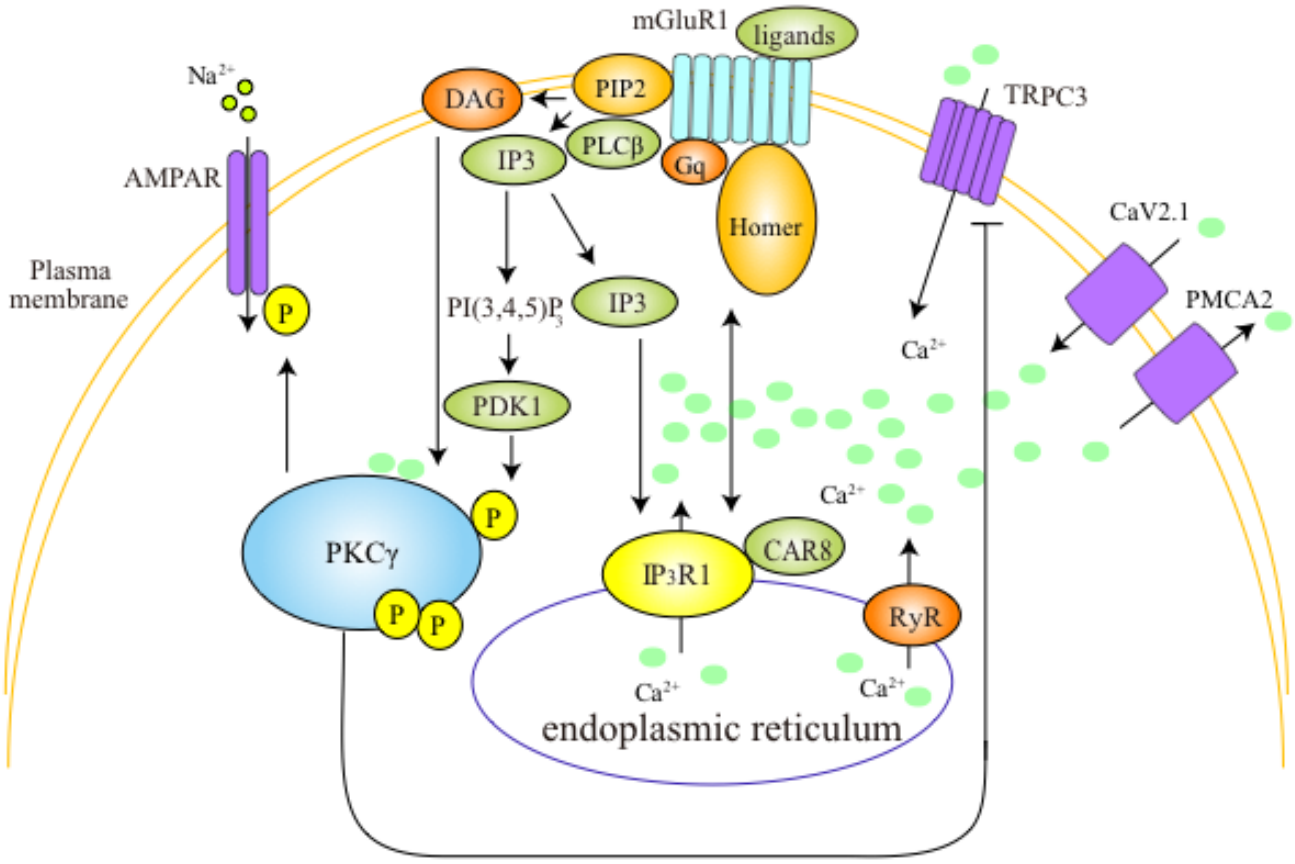

Fig. (1A). Summary of the PKCγ calcium-signaling pathway. Ligand binding to the mGluR1 receptor is followed by PLC-mediated hydrolysis of PIP2 into the second messenger IP3 and DAG. Binding of IP3 to the IP_3R1 and induces Ca^{2+} release from the endoplasmic reticulum to the cytoplasm. This step is controlled by CAR8 which can inhibit binding of IP3 to the IP_3R1. Simultaneous binding of Ca^{2+} to the C2 domain and of DAG to the C1 domain induce translocation of PKCγ to the plasma membrane. There, the pseudosubstrate is released from the kinase domain, allowing phosphorylation of downstream target proteins. PKC exerts an inhibitory effect on TRPC3 channel activity directly through phosphorylation or indirectly. A rise of the intracellular calcium concentration can also be mediated by the voltage-gated Ca^{2+}-channel Cav2.1 or TRPC3. Conversely, PMCA2 can efficiently remove Ca^{2+} from the cytoplasm.

confirming the association of both genes to ataxia [76]. Recently it was shown that CAR8 was upregulated in a SCA14 mouse model with increased PKCγ activity [46]. CAR8 overexpression in developing Purkinje cells in dissociated cultures impaired Purkinje cell dendritic development raising the possibility that CAR8 might also be a regulator of Purkinje cell dendritic development [46]. There is evidence that CAR8 is associated with the IP$_3$R1 and may modulate IP$_3$R1 function by interfering with binding of IP3 to the IP$_3$R1 [59] although a direct interaction of the two proteins in Purkinje cells has not yet been proven [46]. These findings suggest that the ataxic phenotype of the *wdl* mouse could be explained by a loss of the precise regulation of IP$_3$R1 activity and that the altered activity of the IP$_3$R1 could contribute to the abnormal dendritic development of Purkinje cells.

6. IP$_3$R1, CAR8 AND PKCγ ARE ACTIVE IN A COMMON SIGNALING PATHWAY

IP$_3$R1, CAR8 and PKCγ proteins are all known to be strongly and specifically expressed in Purkinje cells [46, 77-80]. The common function among them is that they are involved in Ca^{2+} influx to the cytoplasm and in the regulation of Ca^{2+} homeostasis in Purkinje cells [29, 59, 81]. As mentioned, Ca^{2+} signaling is a key factor for both, Purkinje cell dendritic development and the pathogenesis of SCA. As depicted in Fig. (**1A**), Ca^{2+} signaling is initiated through Ca^{2+} channels and external stimuli acting upon membrane receptors (*i.e.* G-protein-coupled receptors or receptor tyrosine kinases), followed by phospholipase C (PLC)-mediated hydrolysis of phosphatidylinositol 4, 5-bisphosphate (PIP2) into the second messengers IP3 and DAG [82]. This pathway is dynamically controlled by feedback loops which control the IP3 level and metabolism as well as IP$_3$R1 function [83-84]. At basal levels of IP3, cytoplasmic Ca^{2+} levels are maintained by influx and efflux from the endoplasmic reticulum (ER) and the plasma membrane. Once PLC-mediated IP3 and DAG production has occurred, IP3 binds to the IP$_3$R1 and increases the Ca^{2+} influx to the cytoplasm from the ER. The simultaneous elevation of the Ca^{2+} concentration and DAG in the cytoplasm activates PKCγ which in turn phosphorylates its substrates [85]. However, the majority of the well characterized substrate proteins do not seem to be directly associated with SCA14 pathogenesis [40]. It is known that the IP$_3$R1 is a target of PKC phosphorylation and that phosphorylation promotes the IP3-induced calcium release [86]. This suggests that PKC-mediated phosphorylation of the IP$_3$R1 may form part of a positive feedback loop. Activated PKCγ phosphorylates TRPC3-channels which reduces Ca^{2+} influx from the plasma membrane through these channels and limits the Ca^{2+} concentration in the cytoplasm [29,

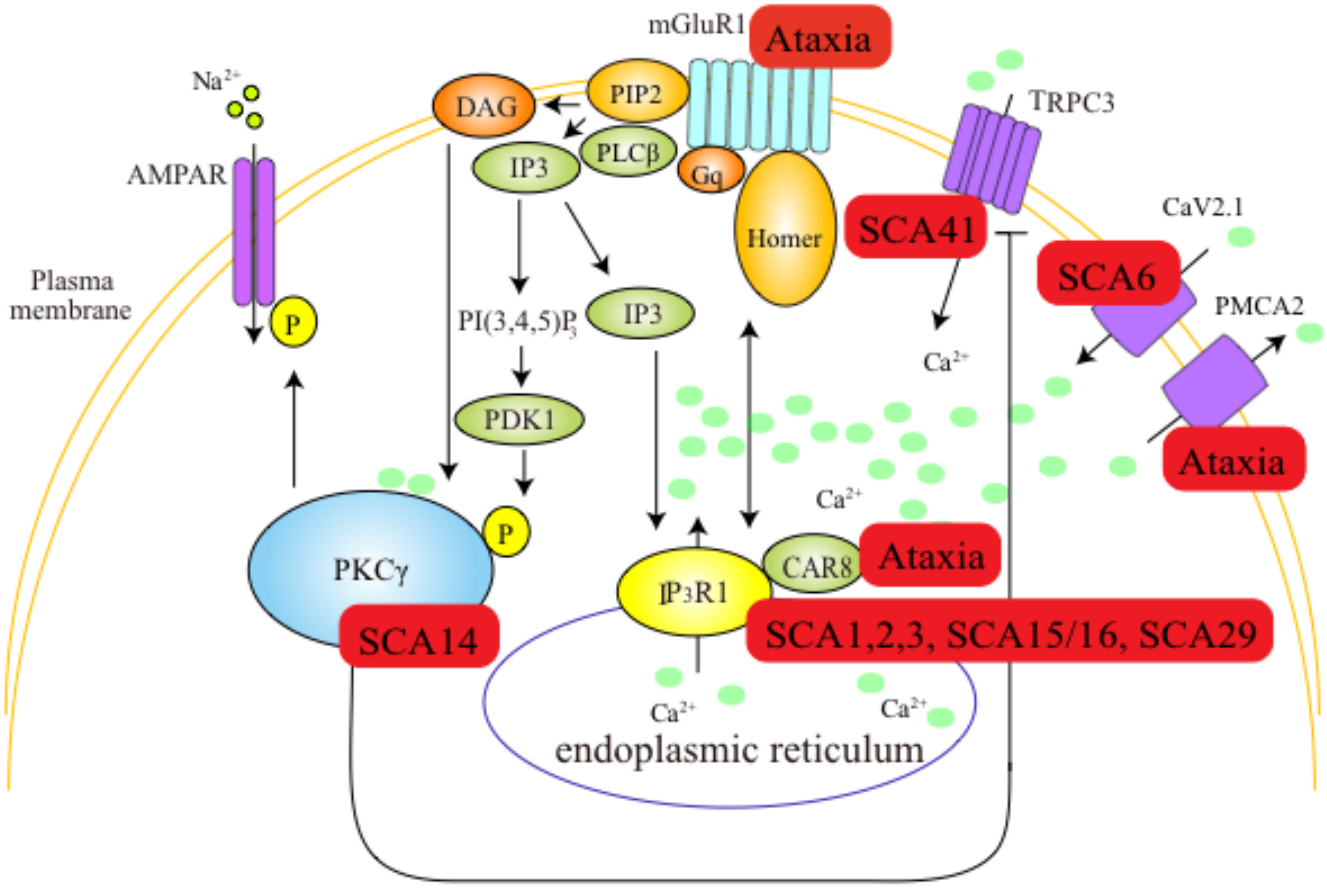

Fig. (1B). Many proteins of the PKCγ calcium signaling pathway are targets of mutations causing ataxia. Mutations causing cerebellar ataxia often have proteins of the PKCγ calcium signaling pathway as targets (shown in red). This highlights the importance of this pathway for the appropriate function of cerebellar Purkinje cells.

87]. As discussed above, one mutation related to SCA14 was recently shown to result in a constitutive active form of PKCγ causing abnormal dendritic development of Purkinje cells linking an increased PKC activity to the pathogenesis of ataxia [45]. Moreover, the IP_3R1 and CAR8 are upregulated in this SCA14 mouse model carrying the mutant PKCγ protein with higher kinase activity [46]. The upregulation of CAR8 may appear somewhat surprising because CAR8 is thought to be a negative regulator of IP_3R1 [59] and would be antagonizing the increased IP_3R1 expression. However, the increased expression of CAR8 could reflect a negative feedback loop for controlling Ca^{2+} homeostasis, and thus would be the logical consequence of the increased IP_3R1 expression.

CONCLUSION

Overall, the IP_3R1, CAR8 and PKCγ related ataxic phenotypes could in part be explained by changes in IP_3R1 activity leading to poorly controlled Ca^{2+} influx/efflux and poor control of the Ca^{2+} concentration in the cytoplasm. This concept is supported by the finding that mutations affecting the function of various molecules involved in this signaling pathway will cause several subtypes of SCA or other forms of cerebellar ataxia (Fig. **1B**). Once PKCγ- IP_3R1 related Ca^{2+} signaling is disturbed the normal dendritic development of Purkinje cells is impaired as well as the integration of signals from other neurons, resulting in abnormal development, cerebellar dysfunction and eventually Purkinje cell loss.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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