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From mice to men: TRPC3 in cerebellar ataxia

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Abstract

The dominantly inherited cerebellar ataxias are a clinically and genetically heterogeneous group of neurodegenerative disorders. Studies using mouse models as well as recent genetic and transcriptomic human findings point to an important role for TRPC3 signaling in cerebellar ataxia.

The autosomal dominantly inherited spinocerebellar ataxias (SCAs) are a heterogeneous group of degenerative disorders characterized by progressive cerebellar dysfunction resulting primarily in gait and limb incoordination. Additional features may be present and include extrapyramidal features, long tract signs, peripheral neuropathy, as well as, in some cases, cognitive impairment and seizures. Currently, more than 35 distinct genetic loci have been identified to cause SCAs [1]. However, about half of the SCA patients do not have mutations in the known genes, suggesting that many more disease genes await identification.

One of the novel genes emerging in cerebellar ataxia is *TRPC3*. The *TRPC3* gene encodes a sodium- and calcium-permeable ion channel of the transient receptor potential (TRP) family, which is highly expressed in the Purkinje cells of the cerebellum, starting within the first postnatal week (reviewed in [2]). Functionally, TRPC3 is required for metabotropic glutamate receptor subtype 1 (mGluR1)-dependent synaptic transmission in Purkinje cells [3] and might also be important for the induction of long-term depression (LTD) [4]. Moreover, a recent study has linked differences in the intrinsic firing activity of Purkinje cells present in cerebellar modules to differential activity of TRPC3 [5].

Both, genetic loss of *Tpc3* as well as the dominant *Moonwalker* (*Mwk*) gain-of-function point mutation in *Tpc3* result in cerebellar ataxia in the mouse [3,6]. These findings underscore the importance of the TRPC3 channel for homeostasis and Purkinje cell function. Interestingly, besides adult-onset Purkinje cell loss, the *Mwk* mutation in TRPC3 causes impairments in Purkinje cell dendritic arborization during cerebellar development [6]. This observation adds to the increasing evidence that altered neurodevelopmental processes contribute to neurodegenerative diseases including SCAs. Moreover, the developmental phenotype in the *Mwk* mice is consistent with other studies demonstrating that chronic activation of Purkinje cell post-synaptic signaling limits dendritic growth [7]. However, the

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Conflict of Interest Notification Page

The author declares no conflict of interest.

downstream effector pathways mediating this activity-dependent inhibitory effect on Purkinje cell arborization remain elusive. To investigate the mechanism(s) underlying *Mwk* TRPC3-mediated impairments in Purkinje cell development, we have carried out transcriptomic profiling in Purkinje cells from mutant animals and wildtype littermates that were isolated by laser capture microdissection (LCM). The forthcoming identified gene targets that were presented at the 6th International Congress of the Society for Research on the Cerebellum (SRC) promise to provide a mechanistic understanding of the pathways that link activated TRPC3 signaling to the regulation of Purkinje cell development in the *Mwk* cerebellum.

In addition to the *Mwk* and *Trpc3* knockout mouse models, disturbed mGluR1-TRPC3 signaling has been identified in several other mouse models of cerebellar ataxia including SCA1 and SCA3 transgenic mice, homozygous *staggerer* mice (*Rora* mutation) and *hotfoot* mutant mice (*Grid2* mutation) (reviewed in [2]). These findings suggest that TRPC3 is a central player in a glutamate-triggered signaling cascade that is vital for Purkinje cell function and, when disrupted, results in cerebellar ataxia (see Figure). This hypothesis is also consistent with a recent transcriptomic analysis of human brain tissue that identified TRPC3 as part of a significant SCA-enriched co-expression module [1]. Based on the accumulating evidence linking TRPC3 to cerebellar ataxia, we wondered whether the *TRPC3* gene itself may be affected in hereditary human cerebellar ataxia. To investigate this interesting possibility, we have performed Sanger sequencing and, more recently, next-generation whole exome sequencing in patients with sporadic-onset cerebellar ataxia [8,9]. Using exome sequencing, we recently identified the first functionally pathogenic variant in the human *TRPC3* gene (p.Arg762His) in a patient with adult-onset cerebellar ataxia [10]. The mutated p.Arg762His lies within the highly conserved TRP domain of TRPC3. Structural modeling as well as functional experiments suggest that this mutation has a significant effect on TRPC3 channel function [10]. Interestingly, the human *TRPC3* variant is likely to act through a toxic gain-of-function mechanism similar to the *Mwk* mutation in mouse. Our study suggests that mutations in *TRPC3* might a rare cause of adult-onset SCA and should be considered for diagnostic next-generation sequencing in the ataxia clinic.

Together, our findings and studies by others suggest that the disruption of TRPC3 signaling might be a common pathologic mechanism underlying cerebellar ataxia in mouse and men. As both, abnormal activation as well as inhibition of TRPC3 signaling result in cerebellar ataxia, the status of mGluR1-TRPC3 signaling should be assessed for individual ataxias. Pharmacological modulation of the TRPC3 pathway might then be an attractive therapeutic approach as it could target neuronal dysfunction early on during the disease. In light of TRPC3 expression in other non-neuronal tissues and possible serious side-effects, ideally any pharmacological modulation should specifically target neuronal TRPC3 function.

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TRPC3 is a key player in the mGluR1 signaling pathway, which is vital for Purkinje cell function. Glutamate released from granule cell terminals binds to the mGluR1 receptor at the Purkinje cell postsynaptic site, which activates phospholipase C/D via Gα protein to produce inositol triphosphate (IP₃) and diacylglycerol (DAG). Prodynorphin (PDYN) expression is inversely correlated with the expression of mGluR1 (dotted line). The GluD2 receptor is associated with a mGluR1-TRPC3-PKCγ signaling complex and might regulate mGluR1-mediated synaptic transmission in cerebellar neurons. IP₃ subsequently binds to its receptor IP₃R1 in the endoplasmic reticulum (ER), resulting in Ca²⁺ release from this intracellular store. Protein kinase C γ (PKCγ) is activated by DAG and Ca²⁺. mGluR1-dependent synaptic depolarization is dependent on TRPC3. TRPC3 can be regulated by DAG, interaction with IP₃R1, and inhibitory phosphorylation by PKCγ (dashed lines). Activation of TRPC3 results in Ca²⁺ influx. TRPC3 is also permeable for Na⁺ ions and might activate voltage-gated calcium channels including Ca_v2.1 through changes in membrane potential (ΔV_m, dashed line). Loss of any component in the depicted signaling cascade results in cerebellar ataxia in human and/or mouse. Names of mutant ataxic mice and human genetic ataxias associated with mutations in genes encoding signaling molecules are indicated in light blue. Gene names that differ from the protein names are shown in parentheses. Knockout mice deficient in the genes encoding mGluR1, Gαq and PLCβ4 also display cerebellar ataxia. Please see [2] for a more detailed review.