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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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Protein kinase N1 is a novel regulator of cerebellar axonal and synaptic development via inhibition of AKT and NeuroD2

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Background: The precise balance of axonal outgrowth and presynaptic maturation is crucial for a correct synapse formation. In our recent work, we have identified protein kinase N1 (PKN1), a serine/ threonine kinase belonging to the protein kinase C superfamily, as a novel key player in fine-tuning this process in cerebellar granule cells (Cgc). The only cerebellar output neuron, the Purkinje cell (PC), receives excitatory input from climbing fibers (CF), originating from inferior olivary nuclei, and parallel fibers (PF), originating from Cgc. The formation of the PF–PC synapse is a hallmark during cerebellar development as it drives the correct segregation of PF and CF territories and is important for motor coordination and cerebellar long-term function. The lengthy process to achieve cerebellar synaptic maturity makes it particularly susceptible to developmental abnormalities, which may finally result in neurodegeneration and disabilities such as cerebellar ataxia.
Methods: We have studied morphological, immunohistochemical and electrophysiological properties of wild-type (WT) and *Pkn1*$^{-/-}$ cerebella derived from young postnatal to adult animals. Furthermore, adult WT and *Pkn1*$^{-/-}$ animals were assessed for motoric deficits in behavioural tests. Cultured Cgc from both genotypes were analysed for axonal length and presynaptic maturation and used to investigate the effect of si-RNA mediated knockdown of AKT.
Results: We could show that PKN1-mediated AKT inhibition during PF growth results in a reduction of NeuroD2 levels, a neurogenic transcription factor preventing presynaptic maturation, and a subsequent increase in presynaptic specifications in Cgc. Consequently, postnatal *Pkn1*$^{-/-}$ animals showed higher AKT/NeuroD2 activity and a defective PF–PC synapse formation, as measured with electrophysiological recordings and immunohistochemical stainings. The long-term effect of *Pkn1* knockout was further seen in cerebellar atrophy and ataxia in adult animals.
Discussion: These exciting new results demonstrate that PKN1 functions as a developmentally active gatekeeper of AKT activity, thereby fine-tuning axonal outgrowth and presynaptic differentiation of Cgc and subsequently the correct PF–PC synapse formation. Results have been described in detail in [1].

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Keywords: neurodevelopment – synapse maturation – cerebellum – protein kinase N1 (PKN1) – NeuroD2 – AKT

Reference

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