TOPICAL Seminar

Date: 16 March
Time: 14.00-14.30
Venue: 1252-204

Jun-ichi Kira
Professor Emeritus
Kyushu University

A novel model of rapidly progressive multiple system atrophy-cerebellar type

Multiple system atrophy (MSA) is a progressive neurodegenerative disease that affects the extrapyramidal, cerebellar, autonomic, and pyramidal systems. Nigrostriatal neuroaxonal degeneration predominates in the parkinsonian variant of MSA (MSA-P), whereas the cerebellar variant (MSA-C) preferentially involves olivopontocerebellar fibers with prominent demyelination. In MSA, α-synuclein (α-syn) accumulates in oligodendrocytes as glial cytoplasmic inclusions (GCIs) and plays a pivotal role in neurodegeneration. Transgenic (Tg) expression of human α-syn in oligodendrocytes has therefore been used to model MSA; however, these models generally exhibit gradually progressive MSA-P–like pathology with nigrostriatal degeneration.

We developed a novel MSA-C model by inducing oligodendrocyte-specific overexpression of human A53T mutant α-synuclein in adult mice using Tet-Off regulation. Tg mice began expressing human α-synuclein at 8 weeks of age, when doxycycline was removed from the diet, and subsequently developed rapidly progressive ataxia around 22 weeks of age, culminating in death at approximately 30 weeks. Tg mice exhibited cytoplasmic spreading of α-syn oligomers in oligodendroglia/myelin, astroglia, and neurons from as early as 9 weeks of age. They also showed prominent demyelination and glial inflammation in the brainstem and cerebellum, closely associated with GCI-like inclusions in oligodendroglia. Microarray analysis revealed a strong inflammatory response and robust cytokine/chemokine production in Tg mice.

Early re-inhibition of human α-syn expression by reintroducing doxycycline at 23 weeks led to full recovery of demyelination, whereas re-inhibition at 27 weeks resulted in persistent demyelination with glial inflammation, despite the resolution of phosphorylated α-synuclein aggregates. Our MSA-C mouse model provides a valuable tool for elucidating the pathomechanisms of MSA-C and for developing effective therapeutic strategies for this condition.

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TOPICAL Seminar

Date: 16 March
Time: 14.30-15.00
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Yuu-chi Kira
Neurology Chief Physician
Kyushu University

Inhibitors of Bruton's tyrosine kinase and sarcoplasmic/endoplasmic reticulum calcium ATPase are effective against aggressive MSA-C

Our new MSA-C mouse model exhibits marked glial inflammation. Using single-cell RNA sequencing of CD11b-positive microglia isolated from the brainstem/cerebellum and spinal cord of Tg mice, we identified a unique microglial cluster that highly expresses Toll-like receptor 2 and various inflammatory cytokines compared with other clusters. These microglia surrounded phosphorylated α-synuclein aggregates and also expressed Bruton's tyrosine kinase (BTK) and NOD-like receptor family pyrin domain-containing 3 (NLRP3). We designated these cells as α-synucleinopathy-associated microglia (SAM).

Tolebrutinib and remibrutinib, centrally and peripherally acting BTK inhibitors (BTKi), respectively, were orally administered to Tg mice four times per week from 18 to 26 weeks of age. Tolebrutinib, but not remibrutinib, improved clinical scores and rotarod performance in Tg mice compared with vehicle-treated controls. Immunostaining for BTK showed a significant reduction in BTK-positive microglia in tolebrutinib-treated mice relative to vehicle-treated mice. Both α-syn oligomers and phosphorylated α-synuclein aggregates were markedly decreased in tolebrutinib-treated, but not vehicle-treated, Tg mice. Moreover, BTK-positive microglia were increased in the brainstem and cerebellum of autopsied patients with MSA-C. These findings suggest that a centrally acting BTKi could serve as a novel therapeutic strategy for rapidly progressive MSA-C by suppressing SAM.

In addition, a novel sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) inhibitor, SYN4569, markedly attenuated clinical deterioration and improved rotarod performance from 22 to 26 weeks compared with vehicle. Phosphorylated α-syn-positive and Iba-1-positive areas were significantly reduced in SYN4569-treated Tg mice relative to vehicle-treated Tg mice. MBP-positive areas were better preserved in SYN4569-treated mice than in vehicle-treated mice. These results suggest that intracellular Ca^{2+} dysregulation plays a crucial role in exacerbating MSA-C and that SYN4569 and related compounds may represent promising therapeutic candidates for rapidly progressive MSA-C by restoring Ca^{2+} homeostasis.

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