2018 MEETING

ENCALS

European Network to Cure ALS

20-22 JUNE 2018
OXFORD

BOOK OF ABSTRACTS

C33 Masitinib therapeutically targets sciatic nerve pathology associated with paralysis progression in an inherited ALS model

Emiliano Trias (1), Valentina Varela (1), Romina Barreto-Núñez (1), Sofía Ibarburu (1), Mariángeles Kovacs (1), Ivan C. Moura (2), Olivier Hermine (2), Joseph S. Beckman (3), Luis Barbeito*(1)

Progressive spreading of skeletal muscle paralysis is a clinical feature of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease with an average survival of 2 to 5 years. Evidence in rodent models expressing ALS-linked SOD1 mutations indicate that specific glial and immune cells emerging after paralysis onset can accelerate disease progression. Masitinib inhibition of the tyrosine kinase receptors c-Kit and CSF-1R downregulates activated spinal cord glia cells as well as skeletal muscle mast cells, thus reducing the rate of post-paralysis motor neuron loss, NMJ denervation, and disease progression. However, it is presently unknown whether mast cells and neutrophils play a pathogenic role during spinal nerve degeneration in ALS. We have analyzed the progression of sciatic nerve pathology in SOD1G93A rats from the onset of hind limb paralysis until advanced paralysis over 15 days. We observed a previously unreported infiltration of degranulating mast cells into the endoneurium, the number of which sharply increased after paralysis onset and correlated with progression of nerve pathology. Notably, chymase-positive mast cells formed large heterotypic multicellular aggregates with elastase-positive neutrophils that were aligned along the sciatic nerve endoneurium in close contact with misfolded SOD1 and fragmented myelin ovoids. Mast cells also interacted with macrophages, which expressed the c-Kit receptor ligand stem cell factor (SCF), essential for mast cell differentiation. CSF-1R agonists, IL34 and CSF1, were expressed in GFAP-positive Schwann cells. Pharmacological inhibition of c-Kit and CSF-1R with oral masitinib (30 mg/kg/day) for 15 days from the start of paralysis onset, prevented the appearance of these mast cell/neutrophil aggregates and decreased the number of non-phagocytic macrophages. Remarkably, masitinib treatment also significantly decreased axonal pathology and demyelination, as compared to vehicle-treated rats. These findings provide additional evidence for mast cell and neutrophil-driven pathology of the sciatic nerve in ALS, effectors likely contributing to aggravate distal axonopathy. Moreover, the observation that this disease mechanism can be therapeutically targeted with masitinib provides further rationale for treating ALS with masitinib; its neuroprotective effect having now been reported in both the central and peripheral nervous systems.

1) Institut Pasteur de Montevideo, Uruguay
2) Imagine Institute, Hôpital Necker, Paris, France
3) Linus Pauling Institute, Department of Biochemistry and Biophysics, Oregon State University, Oregon, USA