

PRESS RELEASE

Amyotrophic lateral sclerosis: the active role of Motor Neurons in the immunomodulation

Amyotrophic lateral sclerosis (ALS) is the most common neuromuscular disorder that primarily involves motor neuron cells. Rapid detection of the disease is critical for effective treatment.

The Molecular Neurobiology Laboratory at the Mario Negri Institute has now discovered that the immune molecule CXCL13 is expressed by motor neurons to protect themselves during the progression of ALS. The results will appear online November 5 in the journal *EBioMedicine*.

"This is an interesting and underestimated aspect of neurodegenerative disorders where immune processes are activated in different districts and by different cell types with effects other than those classically known," says Dr Giovanni Nardo, the principal investigator of the study.

Motor Neurons actively induce immune molecules to modulate the surrounding environment

CXCL13 is a chemokine, which is physiologically involved in the organisation of lymphoid organs where immune cells mature. Nevertheless, the expression of CXCL13 in the CNS is strictly associated with neuroinflammation, a pathological feature of several neurodegenerative diseases, including ALS.

The preliminary evidence from the lab showed a significant upregulation of CXCL13 CNS of the ALS mice. At first, this suggested a direct correlation between the activation of the chemokine and a faster disease progression. Unexpectedly, the neutralisation of the chemokine in ALS mice worsened the disease exacerbating the motor neuron impairment and the atrophy of skeletal muscles suggesting a beneficial effect of CXCL13 in ALS.

"The fascinating aspects was that during the disease, motor neurons expressed high levels of this chemokine both at the central and peripheral levels. Thus, the suppression deprived them of a previously unknown protective process. Indeed, we established that the CXCL13 silencing enhanced motor neuron loss and inflammation whilst its administration preserved motor neurons from degeneration," says Dr Trolese, the co-investigator and first author of the paper.

CXCL13 as a prognostic biomarker of ALS

Consistent with the protective action of CXCL13 in mice, the levels of the chemokine were found increased in spinal motor neurons ALS patients while being significantly downregulated in the cerebrospinal fluid (CSF) compared to non-neurological and Multiple Sclerosis patients.

Sede Legale
Mario Negri Milano

Via Mario Negri, 2 - 20156 Milano
Tel. +39 02 390141
mnegri@marionegri.it

Centro di Ricerche Cliniche
per le Malattie Rare "Aldo e Cele Daccò"
Villa Camozzi

Via G.B. Camozzi, 3 - 24020 Ranica (BG)
Tel. +39 035 45351
villacamozzi@marionegri.it

Centro Anna Maria Astori
Parco Scientifico Tecnologico
Kilometro Rosso

Via Stezzano, 87 - 24126 Bergamo
Tel. +39 035 42131
bergamo@marionegri.it

marionegri.it

"Reduced CXCL13 levels in the CSF of ALS patients might be an index of the motor neuron dysfunction, putting this chemokine forward as a clinical adjunct for the early discrimination of the disease compared to ALS-mimic disorders with a high inflammatory component such as chronic inflammatory demyelinating polyneuropathy and multiple sclerosis," says Dr Bendotti, the head of the laboratory.

"The evidence gained by our group introduced an unexpected and peculiar role of CXCL13 in ALS, expressed by motor neurons to prevent inflammation and translocated along with motor axons to prevent their degeneration", Dr Nardo says.

The team is currently working on the development of a proper multi-centric large-scale validation to confirm CXCL13 as an attractive biomarker into clinical practice. In parallel, a more extensive analysis of the processes underlying motoneuronal activation of CXCL13 in ALS will be made to determine the mechanisms hindering inflammation in the CNS and promoting axonal regeneration in the periphery.

The research was mainly funded by Vaccinex Inc. (1895 Mount Hope Avenue, Rochester, NY 14620), together with the "Translating molecular mechanisms into ALS risk and patient's well-being" (TRANS-ALS) - Regione Lombardia (no. 2015-0023).

<https://www.sciencedirect.com/science/article/pii/S2352396420304734>