

expansion, the impaired suppressive functions of ALS Tregs were restored to levels of control Tregs.

Conclusions: Freshly isolated ALS Tregs were dysfunctional and less suppressive than control Tregs. Epigenetically, the reduced suppressive function of Tregs from ALS patients who progress rapidly may be due in part to increased methylation of the TSDR. Since the dysfunction was reversed following expansion, the in-vivo loss of suppression may result from serum or tissue factor modulation *in vivo* and not from irreversible alterations. Autologous adoptive transfer of ex vivo expanded Tregs offers a potentially novel cellular therapy for slowing disease progression in ALS, and a Pilot Safety Trial is now underway.

Acknowledgments: Supported by grants from ALSFindingACure, ALSA, and the MDA.

Reference

1. Henkel JS, et al. *EMBO Mol Med.* 2013;5:64–79.

DOI: 10.1080/21678421.2016.1231971/0095

C96 ACTIVATED IMMUNE RESPONSE IN THE PERIPHERAL NERVOUS SYSTEM IS INSTRUMENTAL TO DELAY THE DISEASE PROGRESSION IN ALS MOUSE MODELS

G Nardo¹, MC Trolese¹, G De Vito^{2,3}, R Cecchi³, N Riva⁴, G Dina⁴, PR Heath⁵, A Quattrini⁴, PJ Shaw⁵, V Piazza³, C Bendotti¹

¹Mario Negri Institute, Milan, Italy, ²Scuola Normale Superiore, Pisa, Italy, ³Center for Nanotechnology Innovation @NEST, Istituto Italiano di Tecnologia, Pisa, Italy, ⁴Neuropathology Unit, Department of Neurology, INSPE, San Raffaele Scientific Institute, DIBIT II, Milan, Italy, ⁵Sheffield Institute for Translational Neuroscience, Department of Neuroscience, Academic Neurology Unit, Faculty of Medicine, Dentistry and Health, Sheffield, UK

Email address for correspondence:
giovanni.nardo@marionegri.it

Keywords: SOD1G93A mice, immune system, peripheral nervous system

The role of the immune system on the progression of amyotrophic lateral sclerosis (ALS) is still controversial being considered either pathogenic or beneficial depending on the context in which it is examined. Recently, we demonstrated that motor neurons (MNs) of C57SOD1G93A mice with slow disease progression activate molecules classically involved in the cross-talk with the immune system. This phenomenon occurs to a lesser extent in 129SvSOD1G93A mice that show a faster disease progression despite expressing the same amount of mutant SOD1 (1). Unexpectedly, neuropathological differences between the fast and slow progressing mice were not found in the loss of lumbar spinal MNs perikaria

but rather in the axonal and neuromuscular compartments (2,3).

Objective: The present study investigated whether and how the immune response is involved in the preservation of motor axons in the mouse model of ALS with a less severe disease course.

Methods: The extent of axonal damage, Schwann cell proliferation and neuromuscular junctions (NMJs) denervation were compared between the two ALS mouse models at the disease onset using immunohistochemical and imaging techniques. Then we compared the expression levels of different immune molecules and the presence of blood derived immune cell infiltrates in the sciatic nerve of the two SOD1G93A mouse strains using immunohistochemical, immunoblot and qRT-PCR techniques.

Results: Muscle denervation, axonal dysregulation, myelin disruption together with a reduced Schwann cell proliferation is prominent in 129SvSOD1G93A compared to C57SOD1G93A mice. This correlates with the faster progression of the disease observed in the first strain. On the contrary, a striking increase of immune molecules, such as CCL2, MHCI and C3, was seen in sciatic nerves of slow progressor C57SOD1G93A mice and this was accompanied by heavy infiltration of CD8+ T lymphocytes and macrophages. These phenomena were barely or not detectable in the peripheral nervous system of fast progressing mice.

Discussion and conclusions: These data show for the first time that damaged MNs in SOD1-related ALS actively recruit immune cells in the peripheral nervous system in order to delay muscle denervation and prolong the lifespan. Thereby, the lack of this response has a negative impact on the disease course.

Acknowledgements: This work was supported by the Motor Neurone Disease Association, Thierry Latran Foundation, Regione Lombardia under Institutional Agreement no. 14501, European Community (FP7/2007-2013) under grant EuroMOTOR no. 259867.

References

1. Nardo G, Iennaco R, Fusi N, Heath PR, et al. *Brain.* 2013;136:3305–32.
2. Marino M, Papa S, Crippa V, et al. *Neurobiol Aging.* 2015;36:492–504.
3. Nardo G, Trolese MC, Tortarolo M, et al. 2016;26:237–47.

DOI: 10.1080/21678421.2016.1231971/0096

C97 EARLY- AND LATE-ACTIVATED MICROGLIA SHOW DISTINCT LOCALIZATIONS AND EXERT DIFFERENT IMPACTS ON TDP-43 PATHOLOGY IN AMYOTROPHIC LATERAL SCLEROSIS SPINAL CORD

S Hayashi^{1,1,2}, R Yamasaki^{1,3}, H Murai^{1,2,3}, K Okamoto^{1,4}, J-I Kira^{1,1}

¹Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, ²Department of Neurology, Gunma Rehabilitation Hospital,