Microglial-axon contacts at the Node of Ranvier in Multiple Sclerosis and EAE : a mechanism involved in early remyelination?

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Abstract

The nodes of Ranvier (NR) are small excitable domains allowing the regeneration of action potentials along myelinated axons. In Multiple Sclerosis (MS), they are affected early but nodal structures can recluster prior to remyelination. We recently showed that NRs are contacted by microglia (MG), the resident immune cells of the central nervous system, and that this interaction is modulated by neuronal activity. Using a demyelinating mouse model, we showed that the interaction is altered in perilesional tissue but increased during remyelination. Disrupting this interaction after demyelination further leads to a decrease of pro-regenerative MG and to impaired remyelination.

We now wish to explore how this interaction could be modulated by the inflammatory component of MS and its inflammatory model.

We thus analyzed in EAE (experimental autoimmune encephalomyelitis) mouse spinal cord the density of MG and monocyte derived macrophages (MDM) and their interaction with NR, compared to controls. MDM infiltration peaks at D17 and correlates with disease activity, while MG numbers are only slightly modified along the disease. At peak, most remaining nodes are engaged by infiltrating MDM, while MG retract from them. However, with remyelination, MG-NR contact is significantly enhanced, in accordance with our previous findings. The extent of this contact in early remyelination is independent of microglial and nodal density, but correlates with clinical recovery in mice.

We further analyzed MG interaction with the nodes in human post-mortem brain tissue (control, NAWM, peri-plaque and shadow plaques) and further assessed MG phenotypes in these various contexts. In shadow plaques, both homeostatic and activated MG were observed and MG-NR contact was enhanced compared to NAWM.

Such observations suggest that microglial contact at the nodes may be involved in early repair process, which is of particular importance as drugs targeting microglial cells are currently developed for MS treatment.