CHARACTERIZATION OF A MOUSE MODEL OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS AND EFFECTS OF NEUROPROTECTIVE STRATEGIES ON DISEASE EVOLUTION

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Background: Progressive multiple sclerosis (PMS) is a devastating disorder characterized by a complex interplay between immune and neural cells, leading to inexorable accumulation of disability and death. The neuroimmune interactions responsible for disease progression still wait to be deciphered at the cellular and molecular levels. A large body of evidence indicates that early mitochondrial dysfunction occurs within the CNS of PMS patients but the therapeutic potential of drugs improving mitochondrial efficiency remains to be defined (Dutta et al., 2006; Witte et al., 2013). The aim of our study is to gather molecular and cellular information on the EAE NOD mouse model and evaluate the effects of clinically-relevant bioenergetic boosting drugs on disease evolution. In particular, we studied the effects of drugs such as bezafibrate, able to promote mitochondriogenesis (Komen and Thorburn, 2014), biotin, a well-known vitamin currently evaluated in clinical trials for PMS therapy but, surprisingly, never tested in EAE models (Tourbah et al., 2018), and dexpramipexole, able to improve the efficiency of mitochondrial F1Fo ATP-synthase (Alavian et al., 2015; Jonas et al., 2015).

Methods: Female NOD mice were immunized with MOG_{35-55}. Functional, immune and neuropathological parameters were analyzed during disease evolution. The effects of a daily treatment with bezafibrate, biotin and dexpramipexole were evaluated.

Results: We found that disease evolution in NOD mice is similar to that of primary progressive MS and is characterized by severe neurodegeneration in the spinal cord. T but not B or NK cell spinal cord infiltrates linearly increase with time but their reduction by dexamethasone does not affect disease evolution. mtDNA, mitochondrial morphology and transcripts for respiratory complex subunits are reduced at early disease stages in spinal cord. Unfortunately, neither bezafibrate nor biotin treatment affects disease evolution. Interestingly, dexpramipexole delays disability progression, reduces spinal cord axonal loss and extends survival in mice with primary progressive EAE.

Conclusion: EAE in NOD mice is featured by early mitochondrial dysfunction and neuroimmune infiltrates apparently secondary to neurodegeneration. Among mitochondria boosting drugs, only dexpramipexole affects disease evolution. Data suggest that the EAE NOD mouse model recapitulates primary progressive MS, and can be harnessed to develop innovative therapies to counteract disease evolution.