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Computerized behavioral assessments of novel model of multiple sclerosis

Multiple sclerosis is an autoimmune disease of the central nervous system. Recently, we have discovered an endogenous pathway that limits inflammation multiple sclerosis-like disease in mice. One of the key molecules of these pathways is Nlrx1 that belongs to Nlr family of proteins. Nlrs bind multiple proteins inside cells thus redirecting molecular signaling. Using state-of-the-art automated behavioral platform, we demonstrate that Nlrx1 inhibit progression of the diseases in a mouse model of MS. Furthermore, we were able to construct mice with increased predisposition to MS. These mice demonstrate the spontaneous appearance of the disease without any immunization. This model helped us to dissociate sickness behavioral profile from the behavioral signature of neuroinflammation. In addition, our results suggest that predisposition may rise from the disturbed homeostasis in the central nervous system rather than the peripheral activation of immune system. We observed that the inflammatory effect of Nlrx1 at the mitochondrial level, in inflammatory cells such as microglia and astrocytes, results in inhibition of assembly of proinflammatory pathways including Type I interferon and NFkB. Accordingly, we observed the reduction in the expression of iNOS, cytokines including IL-1beta and TNF-alpha during microglial activation. In neurons, Nlrx1 effect results in inhibition of necrosis and increased viability. Using N2A cell line, we demonstrated that Nlrx1 protects cells from rotenone toxicity. We demonstrated that Nlrx1 overexpressing cells were more viable than Nlrx1 KO cells and the ratio of apoptosis to necrosis was shifted to necrosis in cells that lacked Nlrx1. In conclusion, our study demonstrates that targeting central nervous system innate immune responses presents promising novel strategy treatments of multiple sclerosis.

Speaker Biography

Denis Gris has started his scientific career with the Master's and PhD in Neuroscience at Dr. Lynn Weaver's laboratory at the University of Western Ontario. He studied the role of inflammation in spinal cord injury. He discovered that the influx of neutrophils is detrimental for recovering after spinal cord injury. Using anti CD11d antibody as a treatment, he demonstrated that animals recovered faster and better after the treatment. Also, he showed that sever spinal cord injury results in massive inflammatory reactions throughout the body leading to syndrome similar to multiple organ dysfunction syndrome. He continued his education in Dr. Jenny P-Y Ting's laboratory as a Post-doctoral fellow at the University of North Carolina at Chapel Hill. There, he studied in detail mechanism of activation of innate and adoptive immune responses. In collaboration with Dr. Wen, Dr. Eitas, Dr. Allen, and other members of the laboratory, he studied inflammation during obesity which leads to insulin resistance; innate and adoptive responses during multiple sclerosis. In summary, his role in this laboratory was to define the role of novel family of immuno regulatory proteins (NLRs) in different human diseases. Currently, he is a member of Immunology Program at the University of Sherbrooke and is studying neuro-immune interactions during healthy state and disease.

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