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The role of NLRs in a new spontaneous mouse model of multiple sclerosis

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Many members of NLR family of proteins play an important role in human diseases including diabetes, Crohn's disease, cancer, etc. NLRs bind multiple proteins inside cells, thus redirecting molecular signaling. We concentrated on the role of anti-inflammatory NLRs in multiple sclerosis. Using state-of the art automated behavioral platform we demonstrate that NLRX1 and NLRP12 inhibit progression of the diseases in a mouse model of MS. We observed reduced inflammation and improve biochemical and behavioral outcomes of the disease. Furthermore, NLRX1 acts at the level of mitochondria promoting DRP1 dependent mitochondrial fission. In inflammatory cells such as microglia and astrocytes, this results in inhibition of assembly of proinflammatory pathways including type I interferon and NFkB. Accordingly; we observed 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 over-expressing cells were more viable and the ration of apoptosis to necrosis was shifted to necrosis in cells that lacked NLRX1. We confirmed profound role of NLRs by generating mice that spontaneously develop multiple sclerosis-like disease. In conclusion, both NLRX1 and NLP12 decrease inflammatory responses in the CNS and, therefore, present as a target for treatments in neurodegenerative diseases.

Biography

Denis Gris is a Head of Neuroimmunology Laboratory at the University of Sherbrooke, Canada. He has graduated from Dr. Weaver's Laboratory in University of Western Ontario where he studied inflammation after spinal cord injury. He has completed his Post-doctoral studies from the University of North Carolina at Chapel Hills, NC, USA where he began to investigate role of NLRs in neurodegeneration. He is investigating novel computerized methods of evaluating behavioral outcomes of neuro-inflammation. His main interest is to discover novel anti-inflammatory pathways within the central nervous system and use this knowledge to design therapies for neurological diseases including multiple sclerosis amyotrophic lateral sclerosis autism and epilepsy.

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