Bar-Ilan University
Faculty of Medicine

אוניברסיטת בר-אילן
הפקולטה לרפואה

Faculty Seminar

HLA-DR1-mMOG-35-55 treatment of experimental autoimmune encephalomyelitis reduces CNS inflammation, enhances M2 macrophage frequency and promotes neuroprotection

By

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Monday, November 2nd, 2015
at 14:30 in the Auditorium

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CD74, the cell surface form of the MHC class II invariant chain, is a key inflammatory factor that is involved in various immune mediated diseases as part of the Macrophage Migration Inhibitory Factor (MIF) binding complex. However, little is known about the natural regulators of CD74 in this context. In order to study the role of the HLA-DR molecule in regulating CD74, we utilized the HLA-DRα1 domain, which was shown to bind to and downregulate CD74 on $CD11b^{+}$ monocytes. We found that DRα1 directly inhibited binding of MIF to CD74 and blocked its downstream inflammatory effects in the spinal cord of mice with experimental autoimmune encephalomyelitis (EAE) in DR*1501-Tg mice. Potency of the DRα1 domain could be destroyed by trypsin digestion but enhanced by addition of a peptide extension (MOG-35-55 peptide) that provided secondary structure not present in DRα1. We also demonstrate that DRα1-mMOG-35-55 could effectively treat EAE in MHC mismatched C57BL/6 mice by reducing CNS inflammation, potentially mediated in part through an increased frequency of M2 monocytes in spinal cord. Microarray analysis of spinal cord tissue from DRα1-mMOG-35-55 treated vs. Vehicle control mice with EAE revealed decreased expression of large number of pro-inflammatory genes including CD74, NLRP3 and IL-1β and increased expression of genes involved in myelin repair (MBP) and neuroregeneration (HUWE1).

These findings indicate that the DRα1-mMOG-35-55 construct retains therapeutic, anti-inflammatory and neuroprotective activities during treatment of EAE across MHC disparate barriers.