#13: The Ron receptor tyrosine kinase regulates inflammatory response in an experimental model of multiple sclerosis

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In the experimental autoimmune encephalitis (EAE) murine model of multiple sclerosis (MS), both central nervous system (CNS)-resident macrophages (microglia) and infiltrating monocyte-derived macrophages contribute to disease progression. The Ron receptor tyrosine kinase is expressed on tissue resident macrophages including microglia and is involved in regulating inflammatory responses. An in vivo deletion of Ron (Ron KO) promotes inflammatory macrophage activation (M1) and limits a reparative macrophage phenotype (M2). Herein we investigated whether Ron expression plays a critical role in regulating disease progression in EAE. Ron KO mice exhibit delayed onset of EAE (day 14) compared to Wild-Type (WT) (day 10), however Ron KO mice exhibit greater peak severity at onset. Ron KO mice display T-cell mediated peripheral inflammation, as demonstrated by the significant increase in the secretion of interferon gamma (IFNγ) but not IL-17 and IL-10. At day 14, cultured lymph node cells from Ron KO mice exhibit increased expression of M1-macrophage mediated biomarkers iNOS, COX-2, IL-6, IL12B, IL1Î² and TNF-Î±. A likely cause of this increased inflammatory response can in part be attributed to a T-cell mediated increase in IFNγ. Furthermore, CNS tissues from Ron KO mice have increased gene expression of hallmark inflammatory biomarkers, such as iNOS, IL12B and COX-2 at day 14. The results indicate an interplay between the innate and adaptive immune system, in fostering an M1-mediated inflammatory state as the underlying factor for the observed increase in disease severity in Ron KO mice. Maintenance of Ron expressing macrophages could then be a potential therapeutic approach to treating MS symptoms.