Interleukin-11: a mediator of the effects of intravenous immunoglobulin in experimental multiple sclerosis

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INTRODUCTION

A) What is intravenous immunoglobulin (IVIg)?
A therapeutic that is manufactured by pooling immunoglobulins from various donors → administered to patients with a variety of disorders such as immune thrombocytopenia (ITP) and immune deficiency.

B) Is IVIg used to treat multiple sclerosis (MS)?
IVIg provides therapeutic effects for patients with acute multiple sclerosis, including reducing relapse frequency and clinical score.

C) What is interleukin-11 (IL-11)?
IL-11 is a highly pleiotropic cytokine with anti-inflammatory activity, which has been implicated in myelin formation and oligodendrocyte survival.

D) What do we know about IVIg and interleukin-11 (IL-11)?
The mechanism of IVIg effect is unclear. In previous studies, we have demonstrated a dramatic surge (>1000-fold increase) in IL-11 post IVIg injection in a mouse model of ITP. IL-11 receptor knockout (IL-11Rα$^{-/-}$ KO) mice are available to address this question.

HYPOTHESIS

Induction of the anti-inflammatory and immune modulating IL-11 cytokine following IVIg treatment provides the effector mechanism for IVIg in experimental MS.

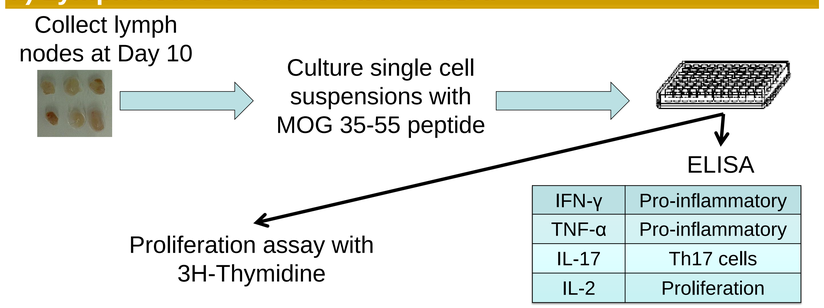
MATERIALS & METHODS

i) Experimental Autoimmune Encephalomyelitis

- **Subcutaneous injection of Complete Freund's Adjuvant (CFA)**
  - Myelin Oligodendrocyte Glycoprotein (MOG 35-55 peptide)
    - Activates peripheral myelin specific CD4$^+$ T cells
    - Capable of crossing the blood brain barrier (BBB)
    - Pro-inflammatory cytokines released ⟶ lesions/tissue damage
  - Pertussis toxin
    - Increases permeability of BBB
    - Enhances cytokine production
- **EAE scoring:**

Score	Symptoms
1	Tail paralysis
2	Weakness in one or both hind limbs
3	Paralysis of one or both limbs
4	Almost complete paralysis of limbs and tail (moribund)
5	Death

ii) Lymph nodes collection and ELISA.



IFN-γ	Pro-inflammatory
TNF-α	Pro-inflammatory
IL-17	Th17 cells
IL-2	Proliferation

RESULTS

i) KO mice are less sensitive to IVIg treatment

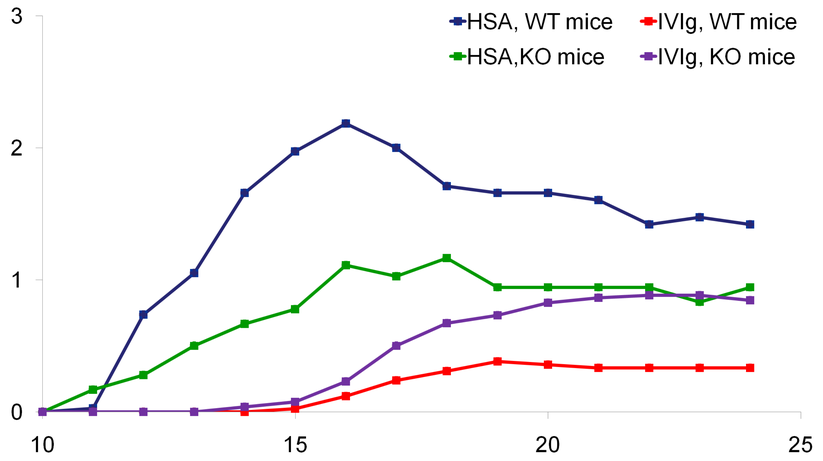


Figure 1. In wild type (WT) mice, IVIg treatment prevented the development of severe EAE as compared to mice injected daily with HSA. IVIg however offered no protective role against EAE in IL-11Rα$^{-/-}$ mice (KO), suggesting that IL-11 serves as an effector in IVIg treatment.

ii) Induction of IL-11 is observed post-IVIg injection.

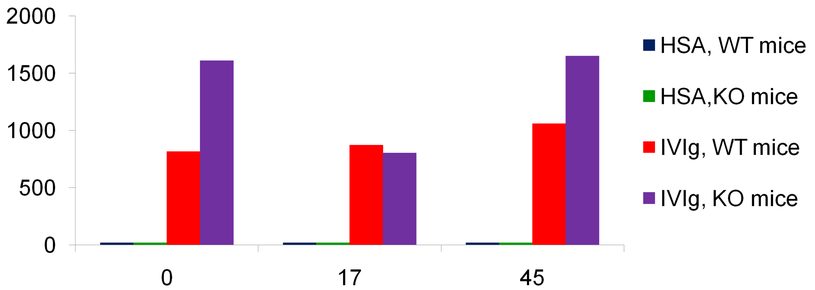


Figure 2. Levels of IL-11 were measured by ELISA 6 hours post-IVIg injection on the days indicated. No IL-11 was detectable in mice injected with HSA, in contrast to higher levels of IL-11 found in both WT and IL-11Rα$^{-/-}$ mice (KO) mice injected with IVIg.

iii) IFN-γ and TNF-α down-regulated with IVIg treatment

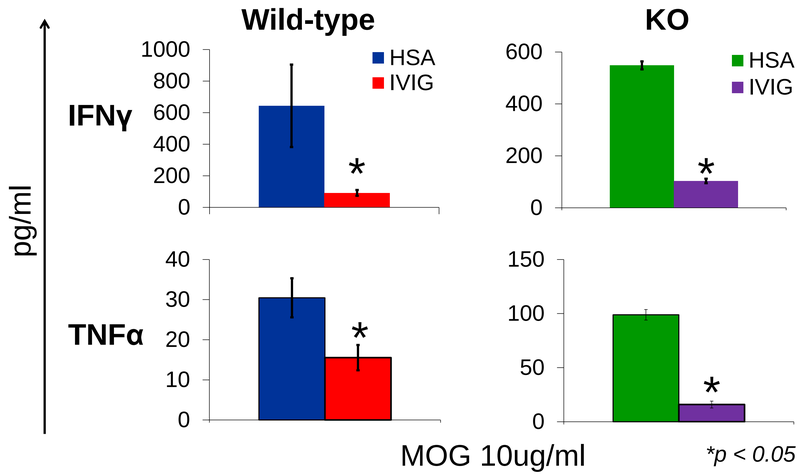


Figure 3. Production of pro-inflammatory cytokines such as IFN-γ, TNF-α weas reduced after IVIg treatment. This was the case for both wild-type and IL-11Rα$^{-/-}$ mice (KO).

iv) IVIg prevents proliferation of T cells

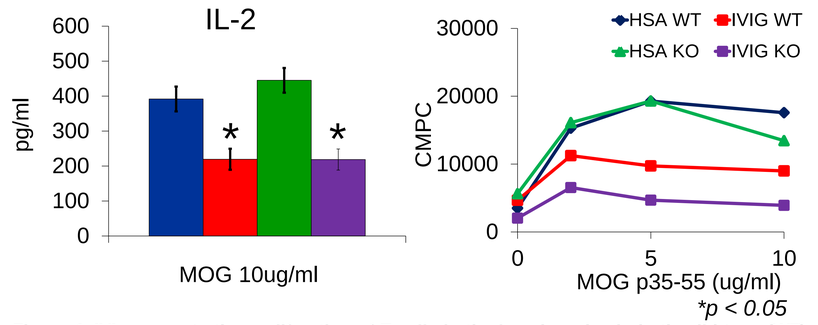


Figure 4. IVIg prevents the proliferation of T cells in the lymph nodes in both wild type (WT) and KO mice. IVIg down-regulates IL-2 as measured by ELISA, and reduces cell counts assessed in 3H-thymidine proliferation assays.

v) IL-11 influences a Th17 type disease in EAE.

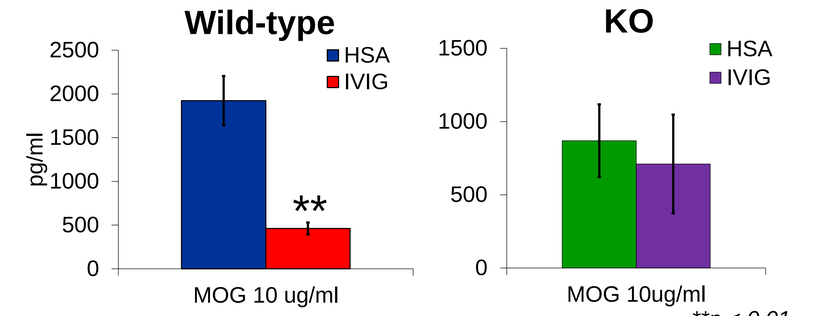
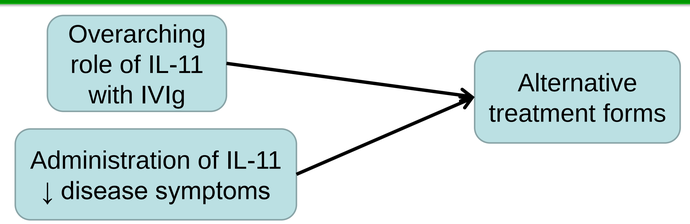


Figure 5. IVIg significantly down-regulates IL-17 in wild type mice. However, in KO mice the levels of IL-17 appeared to be equivocal. This suggesting a potential role for IL-11 in the mechanism of IVIg, in regulating IL-17.

FUTURE DIRECTIONS

1. **Adoptive transfer EAE**
   We will examine closely how IVIg inhibits Th17 biased EAE via IL-11. HSA or IVIg treated cells from WT/KO mice will be adoptively transferred into donor mice with either Th1 or Th17 differentiation.
2. **Trafficking of T cells**
   We have observed in our studies that the lymph nodes of IVIg treated mice are larger than those receiving HSA. We hypothesize that IVIG may work to inhibit the trafficking of T cells to the CNS, thereby preventing the onset of EAE. We will examine the trafficking markers S1P1, CXCR3 and CXCR4 through FACS.

SIGNIFICANCE AND IMPACT



Using alternate treatment options to IVIg may allow for a reduction in costs, as well as the ability to administer drugs without reliance on blood donors and complex production protocols.