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Immune factors in the Neuregulin-1 knockout mouse model of schizophrenia

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BACKGROUND

Schizophrenia

- Neurodevelopmental disorder affecting 1% of the population
- Complex gene x environment interaction
- Neuregulin 1 (Nrg1) gene mutation highly associated in established genetic linkage studies
- Neuregulin-1 heterozygous knockout (Nrg1 KO) mice are an established model of schizophrenia

Schizophrenia and Cytokines

- Cytokines:
  - modulate peripheral immune response
  - can penetrate the blood-brain-barrier (BBB)
  - regulate complex behaviours in healthy brain
- Altered cytokine levels in schizophrenia patients in both blood and CSF
- Cytokine levels correlate with symptom severity
- Epidemiological link between schizophrenia and lower incidence of autoimmune and inflammatory diseases

AIMS

- To determine the basal Nrg1 KO mouse peripheral cytokine profile as observed in schizophrenia patients
- To determine if the peripheral cytokine profile in Nrg1 KO animals is altered following a chronic immune stimulus compared to wild type litter mates

METHODS

Nrg1 KO mice with a heterozygous knockout of the nrg1 transmembrane protein domain on C57/BL6 background

1. Spleen samples obtained:
  a) Adult (PND161) (n=6-15)
  b) Plasma samples obtained:
  a) Late adolescent/early adulthood (PND56) (n=3)
2. Immune challenge:
  a) B16F0 melanoma cell line injected subcutaneously (3x10^6 cells per mouse) (Nrg1 KO and WT littermates; n=8)
  b) Control = PBS injections (Nrg1 KO and WT littermates; n=8)
  c) Late adolescent/early adulthood (PND56)
  d) Sacrifice after 10 days (PND60)
3. Spleen cells analyzed using BD Biosciences fluorescent conjugated antibodies against T and B cell surface markers on LSRII flow cytometry
4. Plasma samples analyzed with multiple flow cytometry bead array to determine levels of IFN-γ, TNF-α, IL-1α, IL-6, IL-2, IL-4, IL-10, and IL-12/23p70

RESULTS

Basal

- B and T cells and their subsets as a percentage of total splenic lymphocytes.
- Representative flow cytometry dot plot of CD4+ cells in the blood and CD4+ cells in the brain

Baseline serum levels of TNF-α, IL-1α, IL-6, IL-2, IL-4, IL-10, and IL-12/23p70 were not associated in our samples

- A tendency towards increased TNF-α, IL-2 and IL-6 (mouse IL-8) indicated a potential pro-inflammatory state in Nrg1 KO animals in the absence of an immune stimulus
- A trend towards decreased IL-10 and IFN-α in the presence of possible increased TNF-α suggested dysfunction of cytokine regulation

This was consistent with data of schizophrenia patients.

DISCUSSION

- IL-6 is produced in the periphery as well as the brain
- IL-6 crosses the blood-brain-barrier from blood to brain via saturable transport mechanisms
- Neurons are responsive to IL-6 signalling - role in neurite outgrowth, differentiation and survival of neurons as well as cognition
- Membrane bound IL-6 receptor has been shown on adult murine and human neurons
- Soluble IL-6 receptor is produced endogenously in brain
- Signal transduction component (gp130) widely distributed in the brain

Relevance to Schizophrenia:
- Patients have consistently demonstrated increased plasma levels of IL-6
- Higher plasma levels of IL-6 have been correlated with worse symptomology
- Anti-psychotics reduce plasma IL-6 levels

First genetic neurodevelopmental mouse model of schizophrenia that mimics the neuro-immunology of the illness.

FUTURE DIRECTIONS

- Acute immune stimulation (LPS)
- Cytokine Microdialysis:
  - measure central IL-6 changes
- Following LPS treatment in Nrg1 KO mice
- Trial result:

Plasma Interleukin-6 levels following B16F0 melanoma challenge in Nrg1 KO compared to WT.

Following a chronic immune stimulus (10 days), the concentration of plasma IL-6 was 20.6 ± 3.2 pg/mL in Nrg1 KO mice compared to 7.6 ± 2.8 pg/mL in wild type litter mates. This represents a 3 fold higher increase in plasma IL-6 levels from control animals in Nrg1 KO mice compared to WT.

Plasma Interleukin-6 following Immune Stimulus in Nrg1 KO and WT mice (pg/mL)

Plasma Interleukin-6 levels following B16F0 melanoma challenge in Nrg1 KO compared to WT.

Induction of IL-6 in the brain due to LPS treatment