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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 genetic linkage studies
  - Neuregulin-1 heterozygous knockout (Nrg1 KO) mice are an established model of schizophrenia1

- Schizophrenia and Cytokines
  - Cytokines: modulate peripheral immune response
  - can penetrate the blood-brain barrier (BBB)
  - regulate complex behaviors 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 C57Bl6 background
- 1. Spleen samples obtained:
  a) Adult (PND161) (n=6-15)
- 2. Plasma samples obtained:
  a) Late adolescent/early adulthood (PND56) (n=3)
- 3. Immune challenge:
  a) B16F04 melanoma cell line injected subcutaneously (3x10⁶ 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 (PND66)
- 4. Spleen cells analyzed using 8-D biosciences fluorescent conjugated antibodies against T and B cell surface markers on LSR1 flow cytometer
- 5. Plasma samples with multiple flow cytometry bead array to determine levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-6, KC (murine IL-4, IL-10 and IL-12/20)

RESULTS

- Basal

- Immune Challenge

Plasma interleukin-6 levels following B16F04 melanoma challenge in Nrg1 KO compared to WT.

- 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

DISCUSSION

- 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 stimulus (LPS)
- Cytokine Microdialysis:
  - measure central IL-6 changes
  - following LPS treatment in Nrg1 KO mice
- Trial result