Fibroblast growth factor signal transduction

A novel therapeutic target for multiple sclerosis

Chris Linington
Developing an effective treatment for multiple sclerosis

Dogma: Chronic inflammatory demyelinating disease driven by a T cell dependent adaptive response originating in the periphery

Reality: Current treatments suppress T cell mediated inflammation in brain but not halt accumulation of disability (Aleumimab, Tysabri)

Why: Disability due to axonal injury/loss caused by inflammatory demyelinating response sequestered in central nervous system

Hypothesis: This inflammatory activity is maintained by T cell independent responses originating within the CNS itself

Strategy – requires getting away from established models and returning to patients

- Identify candidates - analysis of MS lesions/CSF/serum
- Mechanistic studies in vitro
- Validate in vivo – develop new models
- Phase 1 clinical trials – repurposing existing drugs
FGF9 expression is up regulated in MS lesions

**FGF9 Immunohistochemistry**
- Control white matter: negative
- Active lesions: +++
- NAWM: +
- Glial scar tissue: negative

Fold change: 1.22 2.7 22
FGF9 inhibits (re)myelination in vitro

- Oligodendrocyte cell bodies swollen
- Accumulation of MBP & PLP immunoreactivity
- Formation of membranous extensions

Images acquired after ten days exposure (100ng/ml; DIV 18 to 28)
Inhibition of myelination is associated with a pro-inflammatory signature

1752 transcripts upregulated
1510 transcripts downregulated

24 hours
Induction of CCL2 is predominantly astrocytic

HA, hyaluronic acid – surrogate marker for increased activity of hyaluronic acid synthase 2 (Has2 Fold Change > 4)
Induction of TIMP sensitive proteases contribute to inhibition of myelination by FGF9
FGF9 initiates a multifactorial astrocyte-dependent response

- FGF9 – direct mitogenic effect
- Inhibits differentiation

Oligodendrocyte progenitors → Premyelinating oligodendrocyte

- LIF, IL-11, others
- “TIMP” sensitive proteases

- Inhibition

- Pro-inflammatory (?) Innate immune response
What happens in vivo?

- As yet we have no EAE variant that reproduces disease associated changes in FGF9 expression observed in patients
- Binds to the extracellular matrix, short range effect, not detected in CSF

Inject adeno-associated viral vectors encoding FGF9 or EGFP to induce persistent focal expression in astrocytes

Analyse from 10 days till up to 9 months

Christine Stadelmann, Claudia Wrzos, Göttingen
FGF9 expression is retained for at least 9 months
AAV-FGF9 induces a persistent astrocytic response
AVV-FGF9 induces “inflammatory” demyelination

Myelin loss/pallor observed at lesion site 30 days post-injection and becomes progressively more pronounced over time.
Summary

• FGF9 expression increased in MS tissues
  Active lesions > NAWM >> control white matter > glial scar

• In vitro FGF9 inhibits (re)myelination, stimulates OPC proliferation
  modulates multiple functional pathways

• In vivo persistent glial expression of FGF9 induces demyelination and
  inflammation in the adult rat CNS

• FGF9 mediated signal transduction – a novel therapeutic target
  to suppress disease progression in MS?

The unknowns:

• Why induced in MS lesions? Hypoxia?

• At what point are the effects of FGF9 still reversible?

• What is the best therapeutic strategy – selective FGFR inhibitors?
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