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P38 MAPK, A Potential Therapeutic Target for Multiple Sclerosis Treatment

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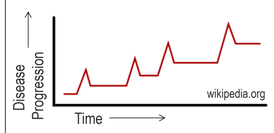
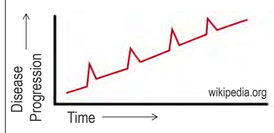
Multiple Sclerosis (MS)

MS Types

Relapsing-remitting MS



Progressive MS



MS Causes

Unknown

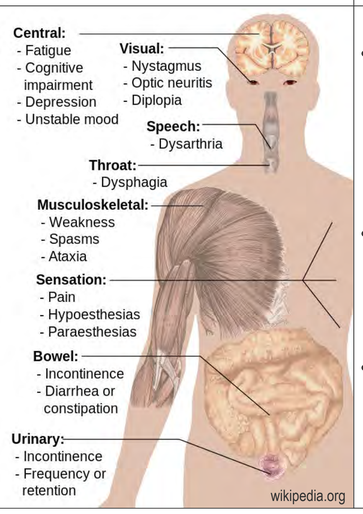
Risk factors

•Genetics
Mutation in genes involved in the human leukocyte antigen (HLA) system, located on chromosome 6.

•Geography
Sun exposure is inversely related to the risk for MS development.

•Infections
Infected by certain viruses, such as Epstein-Barr virus and others, can raise the risk of developing MS.

MS Symptoms

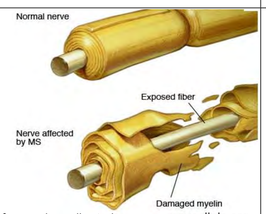


MS Pathology

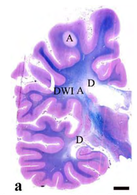
- Inflammation
In the relapsing-remitting stage of MS, initial tissue injury is associated with CD8+ T cells and/or activation of resident microglia attacking myelin which is made by oligodendrocytes. Invasion of T cells, B cells and macrophage through damaged blood-brain barrier causes further myelin deconstruction.

- Blood-brain barrier (BBB) disturbance
A profound damage to the BBB is caused by initial inflammation. BBB rupture is also observed in progressive MS, but its correlation with inflammation is not well understood..

- Plaques
Completely demyelinated regions, demyelinated axons that are embedded in astrocytic scar tissue, and massive loss of axons appear as plaques.



Comparison of normal myelinated axon and myelin deconstruction.



(Lassmann, 2014, Glia)

Coronal section from the brain of a patient with progressive MS. A: New active lesions; D: Completely demyelinated plaques; DWI: Diffuse myelin loss

Treatments

Disease-modifying agents
- Teriflunomide
- Interferon β-1a
- Interferon β-1b
- Glatiramer acetate
- Fingolimod
- Mitoxantrone
- Dimethyl fumarate
- Natalizumb

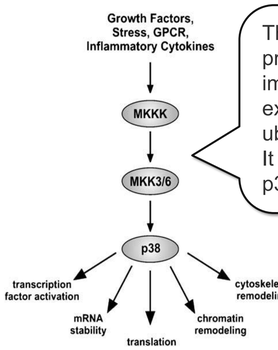
\+ Medication that help to manage the symptoms

No available disease-modifying agents

Only medications that help to manage the symptoms

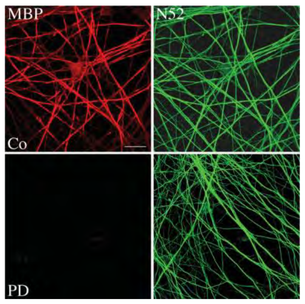
Future Directions

Introduction - P38 MAPK



(Haines et al., 2008, J Mol Neurosci)

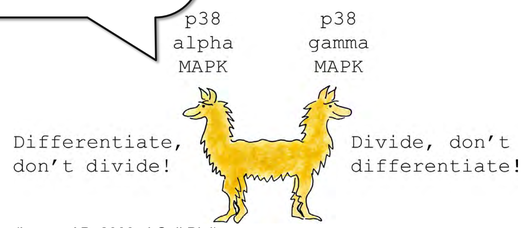
The p38 mitogen-activated protein kinase (MAPK) family is important in response to extracellular signals, expressed ubiquitously throughout the body. It consists of four isoforms: p38α, p38β, p38 γ, and p38δ.



(Fragoso et al., 2007, Glia)

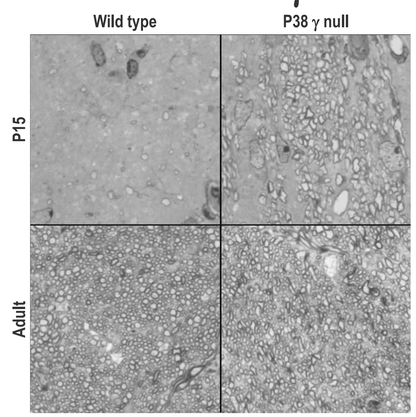
Inhibitors of p38 α block oligodendrocytes differentiation and myelination *in vitro*.

In muscle satellite cells, progenitor cells for muscle, p38γ promotes proliferation and blocks differentiation, while p38 α works in an opposite fashion. We can possibly apply this "pushmi-pullyu" model of alpha and gamma isoforms function to their contribution in myelin formation.



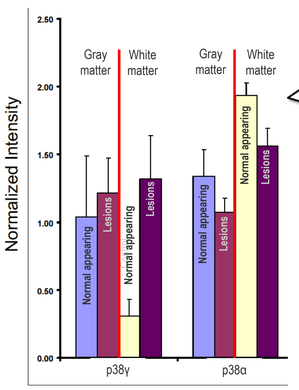
(Lassar AB, 2009, J Cell Biol)

Results - P38γ in Myelination



Semithin sections of corpus callosum (white matter region) from p38γ and p38δ deficient mice

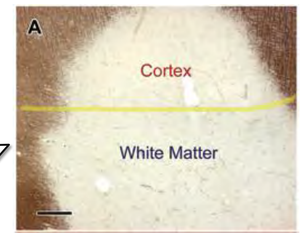
P38γ knocked-out mouse brains show earlier myelination in the corpus callosum, and other white matter areas (data not shown).



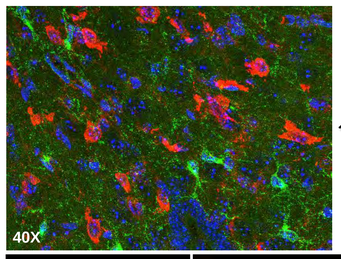
Microarray data from Bruce Trapp lab

P38 γ mRNA level is up-regulated in white matter lesion of MS patients.

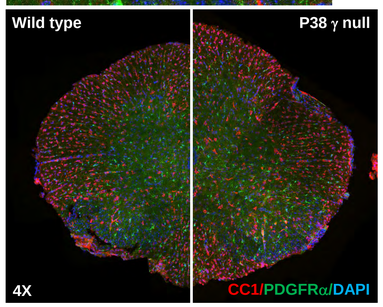
mRNA levels of p38γ and p38α in gray and white matter portions of leukocortical lesions and adjacent normal appearing areas from postmortem brains of 5 patients with MS.



(Ansi Chang et al., Ann Neurol 2012)



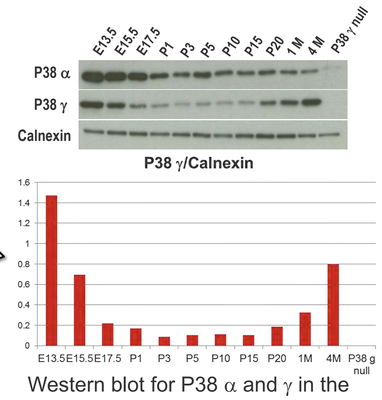
What stage of myelin formation is accelerated in absence of P38 γ ??? Oligodendrocyte maturation? Or myelination?



No striking differences are observed in P14 spinal cord sections.
The project is ongoing, same experiment will be performed on different developmental stages.

Immunofluorescence staining of spinal cord from postnatal 14 days old mice. CC1 is expressed in mature oligodendrocyte. PDGFRα is expressed in oligodendrocyte precursor cells.

P38 γ expression is low during active myelination of the brain.



Western blot for P38 α and γ in the brains from rats at various developmental stage.

Conclusion

- P38 γ deficient mouse brains show earlier myelination.
- P38 γ expression is low during active myelination of the brain.
- P38 γ mRNA level is also up-regulated in white matter lesion of MS patients.
- **P38 γ might be an inhibitor of oligodendrocyte differentiation and/or myelination and also possibly blocking re-myelination in MS patients**.