Expression of P38 MAPK Isoforms During Postnatal Development in The Nervous System

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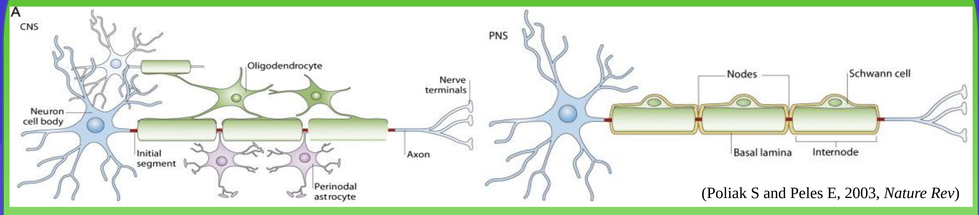
Abstract

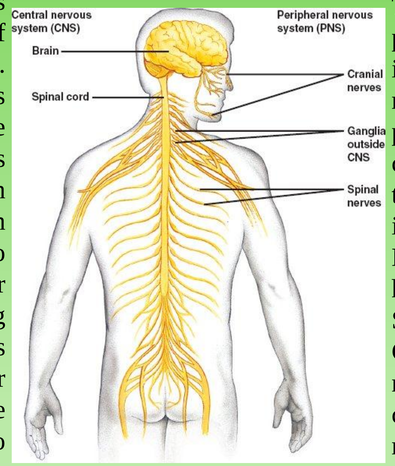
Myelin, a sheath structure surrounding large axons, has a role in protecting axons and enables faster nervous impulse conduction velocity in vertebrates. Myelin sheathes are produced by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). Oligodendrocytes (OLs) can myelinate several axons, whereas Schwann cells (SCs) myelinate only one axon. The p38 mitogen-activated protein kinase (MAPK) family is important in response to extracellular signals. It consists of four isoforms: p38α, p38β, p38γ, and p38δ. The goal of our studies is to understand the role of p38 MAPK in myelination. We have found that p38α is the most abundant isoforms in the nervous system and that p38γ is detected only in differentiating OLs, in contrast, p38δ is produced by OLs under proliferation condition. Interestingly, deletion of p38γ accelerates myelination in the CNS, suggesting that this isoform normally inhibits oligodendrocytes differentiation. My next goal is to determine by immunohistochemistry and Western blot analysis which cell in the brain express the various p38 isoforms, in particular p38γ, and at which developmental time. Through this research, we are identifying all isoforms' specific locations chronographically and geographically to understand how p38γ regulates myelination.

Nervous System



(Poliak S and Peles E, 2003, *Nature Rev*)

The central nervous system (CNS) consists of brain and spinal cord. The spinal cord receives information from the peripheral nervous system (PNS) through sensory neurons and then send to the brain to process. The brain after coordinating incoming information sends actions back to motor neurons through the spinal cord, in order to react.

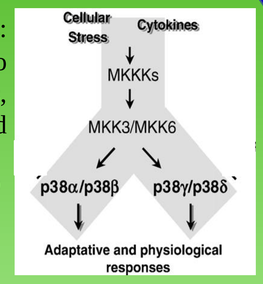


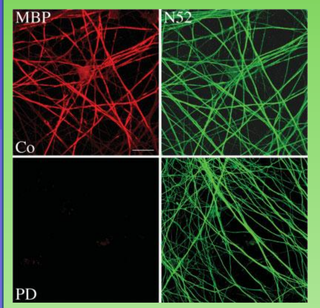
The axons of the neurons are protected and electrically insulated by myelin, a multilamellar structure produced by specialized cells: oligodendrocytes in the CNS and Schwann cells in the PNS.
Myelin is damaged in many human disease, like Multiple Sclerosis, leukodystrophies, Charcot-Marie-Tooth neuropathies. Clarifying the complex mechanism of myelin formation will lead to new therapeutic strategies.

P38 MAPK

P38MAPK family comprises four isoforms: p38α, p38β, p38γ, and p38δ. They response to extracellular signals and environmental stress, and regulates cell migration, proliferation, and differentiation.

(Cuenda A and Rousseau S, 2007, *Biochim Biophys Acta*)





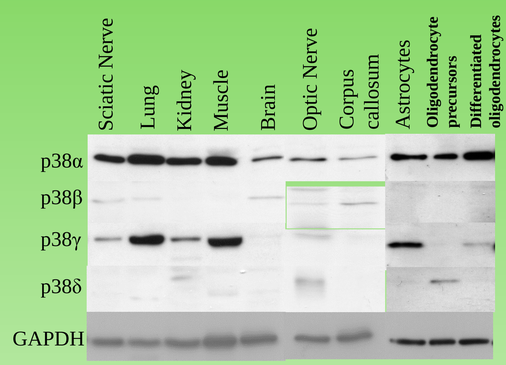
Inhibitors of p38 block oligodendrocytes differentiation and myelination *in vitro*.
(Fragoso et al., 2007, *Glia*)

Aims of the project

- Determine which p38 isoforms are present in the nervous system
- Identify the role of the most interesting isoform in the process of myelination

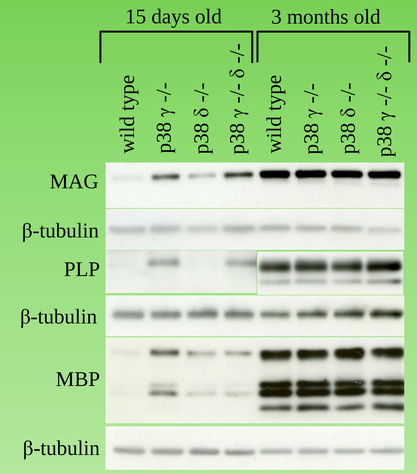
Results in the CNS

p38α and p38β are the most expressed isoforms in whole brain lysates. p38γ and p38δ are enriched in white matter regions (Optic nerve, Corpus callosum). p38γ and p38δ are differently expressed during oligodendrocytes differentiation



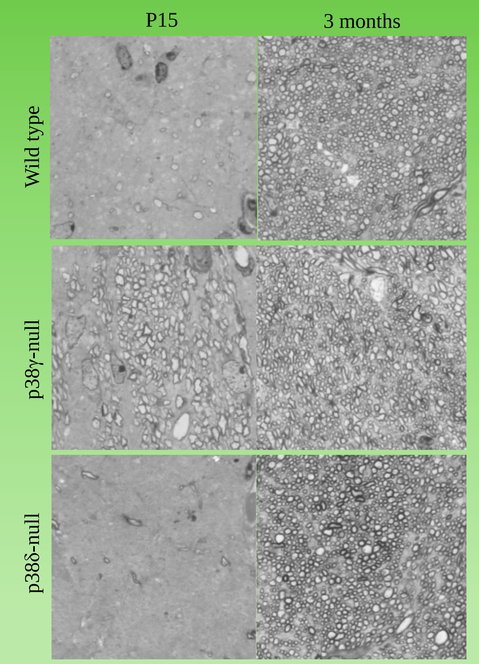
Western blot for p38 isoforms in tissues isolated from adult wild type mice and cells purified from wild type rats

p38γ-deficient developing brains have more myelin proteins in earlier stage of myelination.



Western blot for myelin proteins in brains isolated from p38γ and p38δ-deficient mice

p38γ-deficient brains show earlier myelination in the corpus callosum, but also in the other white matter regions. (Data not shown)



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

Conclusion

- p38α and p38β are the most abundant isoforms in the brain. p38γ and p38δ are enriched in white matter regions and are regulated during oligodendrocytes development.
- p38γ-deficient developing brains have more myelin proteins in earlier stage of myelination.
- p38γ-deficient brains show earlier myelination.
- **p38γ might be an inhibitor of oligodendrocytes differentiation and/or myelination**

Future Directions

- Determine which cells of the brain express p38γ during development
- Determine if the absence of p38γ affects oligodendrocytes number and differentiation state in the brain of the mutant mice