REMYELINATION IN ADULT ANIMAL: NEW APPROACHES FOR MYELIN SHEATH RECOVERY

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INTRODUCTION

Myelin is composed of several layers of lipid-rich membrane that protects the axons enveloping them in both Central Nervous System (CNS) and Peripheral Nervous System (PNS). In CNS, it is produced by oligodendrocytes derived from NG2-glia (polydendrocytes) and its main function is to facilitate the action potentials propagation.

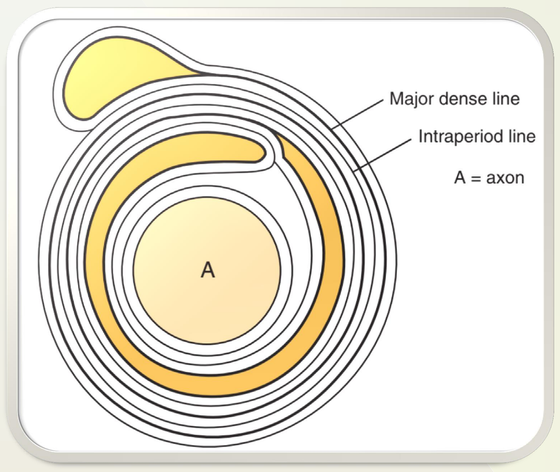

***Figure 1**. Myelin coating pattern around axon (Paidas and Cohen, 1994)*

Loss of myelin, called demyelination, produces functional deficits and may be due to several factors including genetic factors, infectious agents, immunoreactivity and trauma. Demyelination causes an imbalance of axons homeostasis and, consequently, they are more susceptible to degeneration.

OBJECTIVES

- Identification of factors that trigger or difficult physiological remyelination.
- Identification of elements that cause differentiation from polydendrocytes to oligodendrocytes.
- Promote polydendrocytes differentiation to establish a therapy.

REMYELINATION

Polydendrocytes react to any type of demyelinating lesion by changing their morphology and proliferation rate, they migrate to the injured area to repair damaged axons. However, while remyelination in acute lesions is quite successful, it becomes unsatisfactory in chronic lesions as it happens in demyelinating diseases. There are some hypotheses about this fact:

- Polydendrocytes migrate to injured area, but there are lacks of molecular signals, growth factors or an inhibitory environment around the lesion.
- With chronicity, there is an exhaustion of progenitor cells.
- NG2-glia population is heterogeneous in their differentiation capacity.
- Degeneration of demyelinated neurons.
- Presence of antibodies anti-NG2 that harm or destroy the NG2-glia.

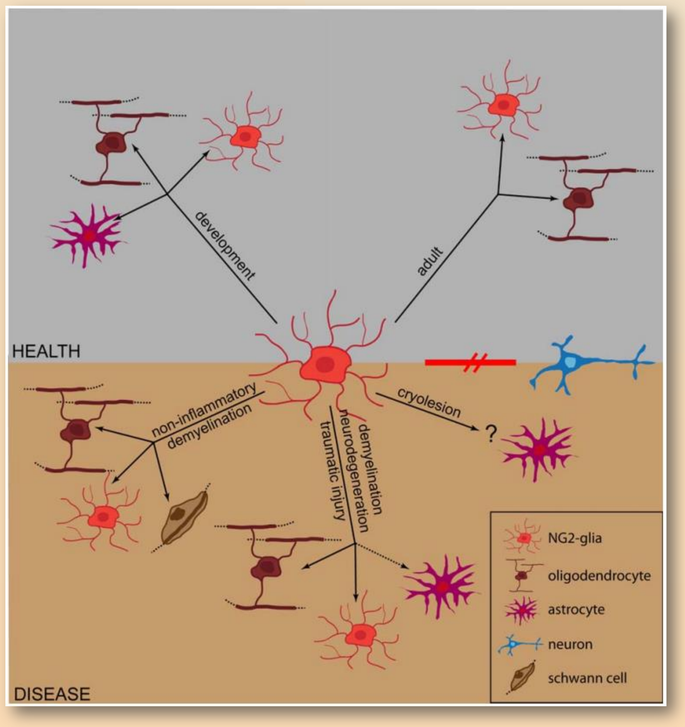

***Figure 2**. NG2-glia differentiation in physiological (top) and pathological (bottom) circumstances (Dimou and Gallo, 2015)*

With aging, oligodendrocytes become less proliferative and lose remyelination potential, axons become vulnerable due to repeated exposures, microglial activity decreases leading debris accumulation and all of that generates an inhibitory environment for myelin sheath regeneration.

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THERAPIES

The main therapeutic strategy is focused on **enhancing polydendrocytes differentiation**, tipping the balance toward the positive regulation above inhibition, especially in cases of demyelinating diseases. Its use can be extended to cases of traumatic injury, ischemia, excitotoxicity and/or viral infection and it has also been attempted to use its neural differentiation to produce neurogenesis.

Cell transplantation: Stem Cells and Olfactory Ensheathing Cells (OECs)

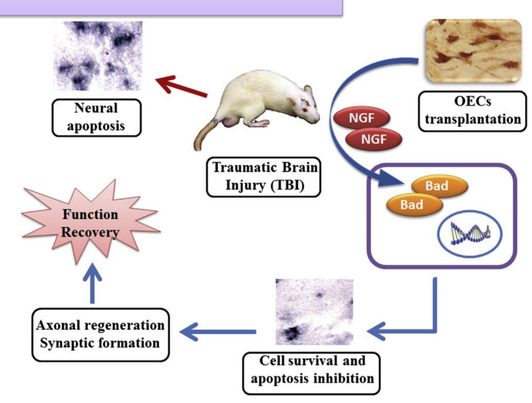

***Figure 3.** Regenerative role of OECs transplantation in a case of traumatic brain injury (Wang et al., 2014)*

Growth and Transcription Factors

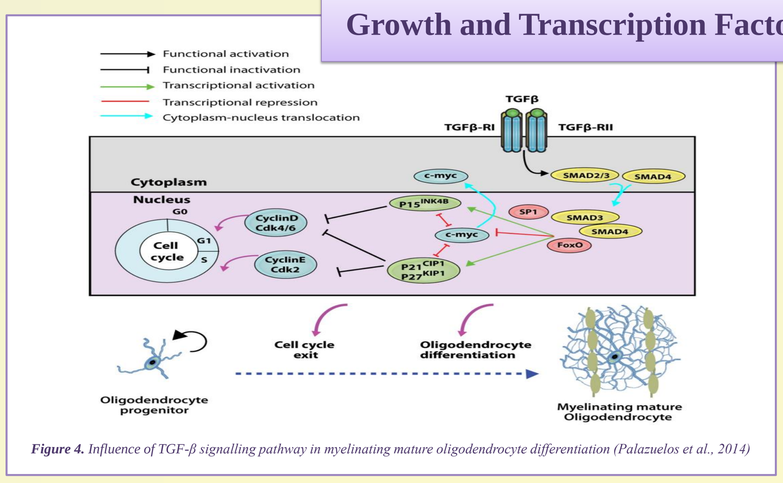

***Figure 4.** Influence of TGF-β signalling pathway in myelinating mature oligodendrocyte differentiation (Palazuelos et al., 2014)*

Immune System

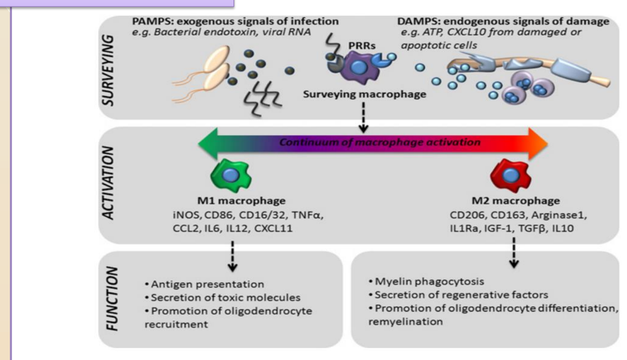

***Figure 5.** Microglial activation and function depending on microenvironment signals from pathogens or cell damage (Miron and Franklin, 2014)*

Drugs

DRUG	ACTION MECHANISM
Benztropine	Blocks Notch signaling, an inhibitory pathway for oligodendroglial differentiation.
Quercetin	Flavonoid molecule that acts as an inhibitor by reducing the cleavage of the Notch receptor intracellular domain.
Quetiapine fumarate	Its fumarate portion directly protects oligodendroglial cells from oxidative stress.
Indomethacin	NSAID that diminishes β-catenin activity promoting polydendrocytes differentiation.
CDP-choline	Important metabolite for plasma membrane synthesis, it enhances phosphatidylcholine synthesis which constitutes an integral part of myelin.
BIIB033	Monoclonal antibody developed to neutralize LINGO-1, an inhibitory receptor for remyelination.
Olesoxime	Cholesterol-like small molecule that binds to two components of the mitochondria in oligodendrocytes and exerts a primarily glioprotective effect.
IgG4 anti-Semaphorin 4D	Blocks Semaphoring, which inhibits polydendrocytes differentiation and worsens clinical signs via blood–brain barrier breakdown induction.
High-dose biotin	Activates myelin formation in oligodendrocytes through its role as a cofactor for acetyl-CoA.

***Table 1.** Some of the drugs tested related with myelin repair (data obtained from Kremer et al., 2016)*

CONCLUSIONS

Polydendrocytes represent a promising therapeutic target because oligodendrocytes derived from them protect axons integrity; however, further studies are needed to know all details about its molecular mechanisms, their recruitment and differentiation.

Numerous extrinsic signals have been identified that can influence polydendrocytes proliferation such as paracrine factors, neurotransmitters, molecules on the cell surface and extracellular matrix and interactions between neurons and NG2-glia.

Replacement of treatments that require cell/genetic manipulation for drug delivery is a very promising therapeutic strategy because it would provide better accessibility, easier and cheaper treatment.