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Scientific Article Summary

Article:
"Dysregulation of the Wnt pathway inhibits timely myelination
and remyelination on the mammalian CNS"

The research article, "Dysregulation of the Wnt pathway inhibits timely myelination and remyelination on the mammalian CNS" discusses the potential causes of progressive loss of CNS (Central Nervous System) myelin. The study is framed around the idea that the loss of myelin is the result from the effects of damage to oligodendrocytes and failure of remyelination. The study had a focus on the effects of dysregulation of the Wnt pathway and its effect on Multiple Sclerosis (MS) patients. The study shows that dysregulation of the Wnt pathway signaling in oligodendrocyte precursors (OLPs) results in the delay and inhibits signaling of both the developmental myelination and remyelination. This conclusion suggests that this dysregulation might contribute in inefficient myelin repair in MS and other human neurological disorders.

Oligodendrocytes are the myelinating cells of the Central Nervous System. Myelin sheaths can be regenerated by newly created oligodendrocytes "following the recruitment and differentiation of OLP cells", otherwise known as "remylenation" and is known as "one of the most efficacious regenerative processes in neurobiology". However, in MS patients, the remyelination process does not occur and results in the accumulation of lesions and "contributes to irreversible axon loss and progressive neurological deterioration. The study discusses that OLPs and premyelinating oligodendrocytes in MS lesions suggest "that remyelination is most vulnerable during the differentiation rather than the recruitment phase".

The study included a new review of the whole-genome of “a unique library of 1040 probes for Transcription Factor-encoding genes”. Doing this, allowed the researchers to start anew in their hypothesis and draw new conclusions and further the discussion of causes of lesions and the deterioration of the myelin sheaths in MS patients. A primary review of their results showed about 50 genes with altered expression within the lesions at some of the key stages of myelin repair. The focus was on the gene “Tcf4 because its expression was specific to damaged white matter in the adult CNS”. Tcf4 was not detected in normal white matter but it is expressed in a developing spinal cord and re-expressed following demyelination and remyelination and within active areas of MS lesions of adult CNS. Tcf4 can activate or repress genes of the Wnt pathway through formation of a nucleoprotein complex with β-catenin and other proteins. The study concluded that β-catenin-dependant activation occurs normally during oligodendrocyte development and CNS remyelination.

The study included the analysis of the effects of the β-catenin signaling in the brain of “Olig2cre/Da-Cat” and “APC^{min}” mice. G-ratios of remelinated axons in “Olig2cre/Da-Cat” mice were significantly increased, indicating delayed repair. Also discovered was significant impairment of remyelination in the “APC^{min}” adult mice. β-catenin signaling inhibited developemental myelination and remyelination in the mice. Together, “these findings establish that activation of β-catenin signaling inhibits OLP differentiation and repair after demyelinating injury.” The conclusion was that the failure of remyelination in human MS lesions might occur due to Wnt pathway dysregulation.

The discussion of the study shows that, although new insights into remyelination inhibition may be due to the dysregulation of the Wnt pathway, more research is needed to rule out other possibilities, including “β-catenin-independent roles for Tcf4 in oligodendrocyte development”. Further studies are also needed to better understand Tcf4-catenin function and the interactions of regulatory networks required for optimal remyelination and how these may be dysregulated in MS patients and other

demyelinating diseases. The study in not fully conclusive, but the beginning of many more studies of the Wnt pathwayand its dysregulation.

The study was completed in conjunction with the UK Multiple Sclerosis Tissue Bank, the Imperial College London, the UK Multiple Sclerosis Society and the National Multiple Sclerosis Society (US). The tissues were collected following the ethical approval by the London Multicentre Research Ethics Committee.