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Death receptor deals blow to remyelination

The endogenous capacity of the CNS to repair damaged myelin sheaths is limited, despite the abundance of oligodendrocyte precursor cells (OPCs) in the adult CNS. The development of strategies to boost endogenous remyelination in disorders such as multiple sclerosis therefore requires an understanding of the mechanisms that regulate oligodendrocyte maturation. Mi *et al*. now show that death receptor 6 (DR6; also known as tumour necrosis factor receptor superfamily member 21) is an important negative regulator of oligodendrocyte survival and maturation, and that blocking the activity of DR6 can enhance remyelination.

DR6, like other members of the tumour necrosis factor receptor (TNFR) superfamily, possesses a cytoplasmic 'death domain' that triggers apoptosis upon ligand binding to the receptor. The authors found that DR6 was expressed at high levels in immature OPCs and that its expression was progressively reduced as the cells matured into myelinating oligodendrocytes. Inhibiting the activity of DR6 in OPC cultures through application of small interfering RNAs or expression of a dominant-negative form of this protein increased OPC survival and maturation, whereas overexpression of a constitutively active form of DR6 increased caspase 3-mediated OPC death.

DR6 activity thus appears to limit OPC maturation, suggesting that it might negatively regulate myelination. Indeed, reducing DR6 activity in co-cultures of OPCs and neurons with the dominant-negative form of DR6 or DR6 antibodies enhanced myelination, and similar results were observed in co-cultures containing OPCs from DR6-null mice. To determine whether DR6 has a similar regulatory role in remyelination in the mature nervous system, the authors examined the effects of blocking its activity in two rodent models of demyelination. Rats treated with a DR6 antibody showed greater remyelination and functional recovery than controls following demyelination induced by lysolecithin or experimental autoimmune encephalitis, as did DR6-null mice.

This study shows that DR6 negatively regulates oligodendrocyte survival, maturation and myelinating function in the developing and adult nervous systems. Targeting this receptor, or the as yet unidentified ligand that triggers this activity, may therefore be a useful strategy for enhancing repair in demyelinating diseases such as multiple sclerosis.

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ORIGINAL RESEARCH PAPER Mi, S. *et al.* Death receptor 6 negatively regulates oligodendrocyte survival, maturation and myelination. *Nature Med.* **17**, 816–821 (2011)
FURTHER READING Franklin, R. and ffrench-Constant, C. Remyelination in the CNS: from biology to therapy. *Nature Rev. Neurosci.* **9**, 839–855 (2011)