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TISSUE INHIBITOR OF METALLOPROTEINASES-1: A CRUCIAL MEDIATOR OF REMYELINATION IN A CUPRIZONE MOUSE MODEL

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BACKGROUND:

Multiple sclerosis (MS) is the most common neurological disorder in young adults and develops as a result of a coordinated autoimmune response against the central nervous system. The prime target in this process is myelin, the insulating sheath around axons that guarantees fast and efficient neuronal transmission. **Oligodendrocytes** and their precursor cells initially help in repairing the myelin layers during a process called 'remyelination', but this process gradually fails leading to further disease progression. While MS treatment has revolutionized the last decade, no therapies are available that directly boost remyelination.
We have recently identified that **tissue inhibitor of metalloproteinases-1** (TIMP-1) is highly upregulated during demyelination in the cuprizone mouse model. Therefore, this **study aims to further unravel the role of TIMP-1 in remyelination.**

METHODS:

In this study, TIMP-1 wildtype (WT) and knockout (KO) mice were used. An acute (6w) or chronic (12w) cuprizone model was used to induce demyelination. Following acute demyelination, mice were treated with recombinant TIMP-1 or vehicle (PBS) for 1 week. Remyelination was analyzed by measurement of the visual evoked potential (VEP) latency and using a luxol fast blue or myelin basic protein staining. In addition, demyelinated white matter lesions of MS patients were stained for TIMP-1.

RESULTS:

TIMP-1 gene expression was markedly upregulated following demyelination in the acute cuprizone model. During various phases of remyelination (after 1w, 2w, and 4w), the TIMP-1 level remained elevated although this was less pronounced than during demyelination. Notably, this **upregulation was absent in the chronic cuprizone model**, with no significant increase observed after myelin injury or during recovery.
TIMP-1 KO mice exhibited comparable VEP latency time at baseline or following acute demyelination compared to WT controls. However, TIMP-1 deficiency prolonged the VEP latency time after different remyelination stages (6w+1w; 6w+2w). In line with these data, our

immunohistochemistry data demonstrated similar myelination patterns between TIMP-1 WT and KO mice at baseline and after acute demyelination, but **TIMP-1 deficiency reduced remyelination compared to WT** mice. Importantly, **cuprizone mice treated with TIMP-1** for 1 week after returning on normal chow, showed a **shorter latency time compared to vehicle-treated WT** controls. In addition, we show that TIMP-1 is also expressed in demyelinated white matter lesions of MS patients.

CONCLUSION:

Taken together, these data provide evidence for the important endogenous **role of TIMP-1 in remyelination and support its therapeutic potential** for treating demyelination in the context of MS.