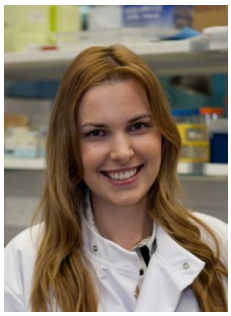
NEW STRATEGY FOR BRAIN REPAIR IN MULTIPLE SCLEROSIS



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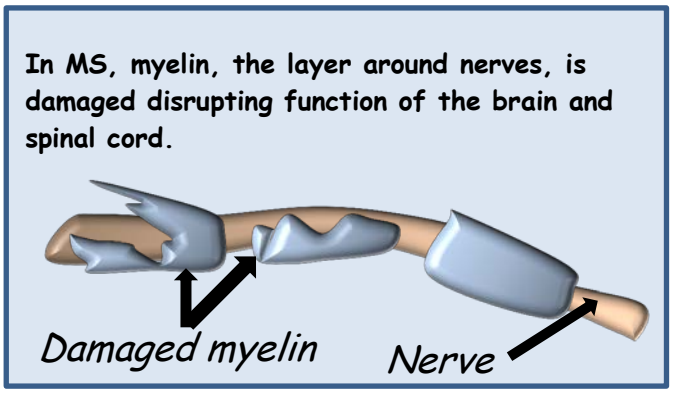
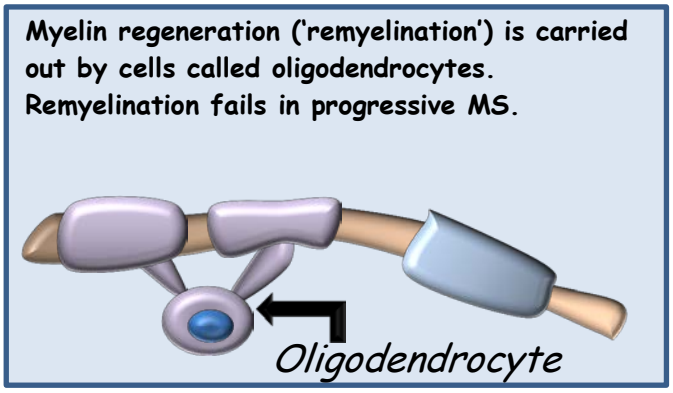
Multiple sclerosis is caused by damage to the insulation around nerves, myelin.

Multiple sclerosis (MS) is the most common disease causing disability in young adults, affecting over 100,000 people in the UK and 2.5 million people worldwide. **In MS the protective layer that surrounds nerves in the brain and spinal cord, called myelin, is destroyed.** This causes nerves to degenerate leading to problems with vision, movement, and speech.



Regeneration of myelin following damage fails in progressive forms of multiple sclerosis.

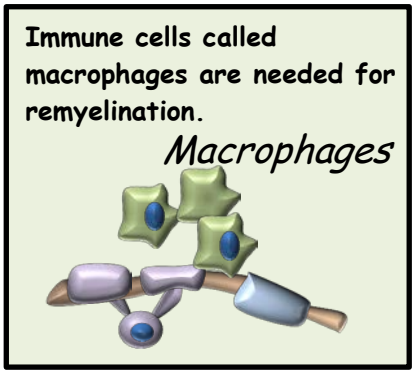
The creation of new myelin ('remyelination') is a regenerative process driven by cells called oligodendrocytes that make the new myelin. **However, remyelination often fails as MS progresses.** This failure leads to the damage of nerves which cannot regrow, causing the loss of function in people with MS. All currently approved therapies for MS only slow disease progression by reducing myelin injury; these are not aimed at promoting remyelination. **Thus, understanding what stimulates remyelination can lead to the discovery of proteins that may be developed into regenerative therapies for the recovery of lost functions in people with MS.**



About multiple sclerosis

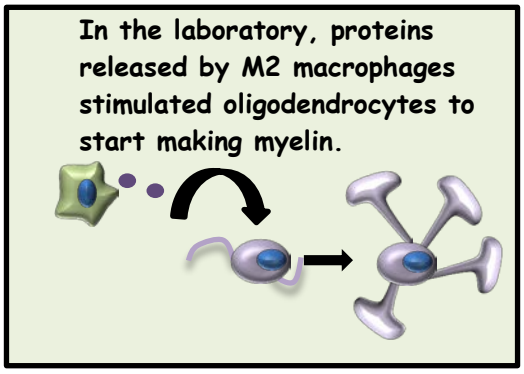
- **Multiple sclerosis (MS) is the most common cause of disability in young adults (mostly aged 15-40), affecting 100 000 people in the UK and 2.5 million people worldwide.**
- **MS is more prevalent in women than in men (estimated to be a 3:1 ratio).**
- **The prevalence of MS increases in areas further away from the equator, e.g. Canada and Scotland have high rates of MS.**
- **Symptoms include problems with vision, hearing, movement, sensation, speech, memory, fatigue, pain, bladder and bowels.**
- **The cause of MS is unknown but likely involves a complex interaction between the environment and genes.**
- **There are different types of MS:**
    - **Most people with MS are diagnosed with Relapse-Remitting MS, where symptoms appear for some time (called a relapse) then improve (called remission).**
    - **Relapse-remitting MS can develop into Secondary Progressive MS where symptoms gradually get worse over time.**
    - **A small number of MS patients show steady accumulation of disability from diagnosis, with or without relapses (Primary Relapsing or Primary Progressive MS).**

Immune cells called macrophages are needed for regeneration.

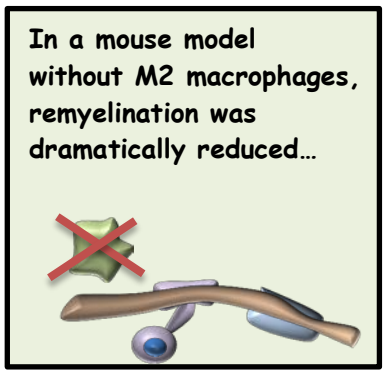


Previous studies have shown that immune cells called macrophages are needed for remyelination to occur. Interestingly, anti-inflammatory macrophages (called 'M2 macrophages') are required for the regeneration of skin and muscle. In a collaborative study between the University of Edinburgh's MRC Centre for Regenerative Medicine and the University of Cambridge's MRC Cambridge Stem Cell Institute, **we examined whether macrophages needed to be anti-inflammatory (M2) to drive myelin regeneration**. We tested whether a protein released by M2 macrophages could stimulate remyelination, which could lead to the development of a new strategy for regeneration in people with MS.

Anti-inflammatory macrophages are required for remyelination.

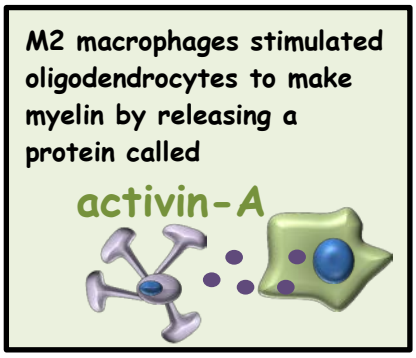


To ask whether M2 macrophages are present during remyelination, we used mouse models of myelin damage and regeneration. **We found that M2 macrophages were present and that they increased in number at the start of remyelination, suggesting that these macrophages may control the regeneration process.** Given that oligodendrocytes are the cells that normally make myelin in the brain and spinal cord, **we asked whether M2 macrophages on their own are able to stimulate oligodendrocytes to start making myelin by exposing them to proteins released by M2 macrophages in the laboratory. These proteins did promote more oligodendrocytes to make myelin**.



To observe whether remyelination could continue in the absence of M2 macrophages, these cells were eliminated following myelin damage. **In a mouse model without M2 macrophages, remyelination was dramatically reduced indicating that M2 macrophages are needed for remyelination.** Analysis of mouse models of remyelination and brain tissue from people with MS showed that numbers of M2 macrophages are high when remyelination is efficient, but not when remyelination is poor.

Macrophages stimulate oligodendrocytes to make myelin by releasing activin-A.

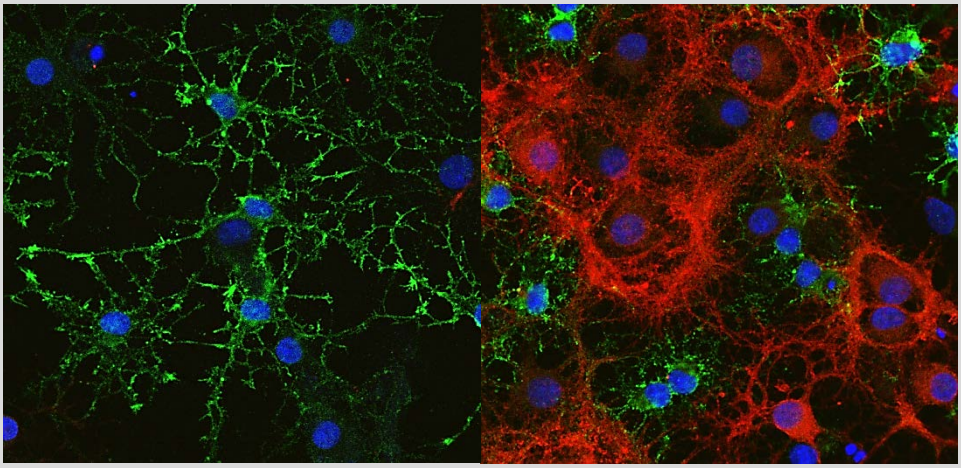


We then tested whether a protein called activin-A, which is produced by macrophages, contributes to the regenerative effects of M2 macrophages. **Activin-A was present at very high levels in M2 macrophages as remyelination was starting, and addition of activin-A to oligodendrocytes in the laboratory stimulated them to make myelin.** By blocking the effect of activin-A on oligodendrocytes following myelin injury, we found that the M2 macrophages had a reduced ability to promote oligodendrocytes to make myelin.

In summary, we showed that M2 macrophages release activin-A which causes oligodendrocytes to make myelin, a key step in myelin regeneration.

Oligodendrocytes in the absence of activin-A are not making myelin.

Oligodendrocytes exposed to proteins released by macrophages including activin-A making myelin



These are our microscope images of oligodendrocytes in the laboratory without activin-A and after treatment with proteins released by macrophages, including activin-A. Oligodendrocytes that are not making myelin are in green. Oligodendrocytes that are starting to make myelin are in red. Treatment of oligodendrocytes with activin-A stimulates them to start making myelin.

How does myelin regeneration happen and why does it fail?

- **The damage to the brain and spinal cord in people with MS is directed at the insulating layer surround nerves, called myelin. Areas of damage are called 'lesions' or 'plaques'.**
- **Creation of new myelin to replace the damaged myelin, called remyelination, occurs at different levels of efficiency in different patients. Usually it is quite effective in early phases of MS (relapse-remitting MS), but often fails in progressive forms of MS.**
- **Remyelination starts by cells (called progenitor cells) moving into the lesion from surrounding areas, becoming new oligodendrocytes, and then creating new myelin around nerves.**
- **Previous studies suggest that remyelination fails in progressive MS because progenitor cells can't move into the lesions, and also can't become oligodendrocytes. This may be caused by proteins in the lesion that prevent oligodendrocytes from moving in and making myelin, or the absence of proteins that allow oligodendrocytes to do these things.**

What does this mean for patients?

The results in this study suggest that studying M2 macrophages and activin-A might offer exciting new opportunities for the development of regenerative therapies for multiple sclerosis. In combination with a drug to reduce the initial myelin damage, therapies developed from these new findings may support regeneration of the central nervous system and restore lost functions in multiple sclerosis patients. Future work is needed to understand how activin-A affects oligodendrocytes and to determine the likely safety and effectiveness of potential therapies in humans before any clinical trial for multiple sclerosis could take place.

Publication details

Miron VE, Boyd A, Zhao J-W, Yuen TJ, Ruckh JM, Shadrach JL, v.Wijngaarden P, Wagers AJ, Williams A, Franklin RJM & ffrench-Constant C. 2013. M2 microglia/ macrophages drive oligodendrocyte differentiation during CNS remyelination. Nature Neuroscience, epub ahead of print.
DOI: 10.1038/nn.3469.