Eating up the central nervous system

Diana Arseni
Institute of Infection, Immunity and Inflammation, University of Glasgow

What is the problem?

Multiple sclerosis (MS) is an autoimmune disease, where the body's immune system attacks itself, rather than harmful agents (such as bacteria and viruses) which it is designed to protect us from. MS affects the central nervous system (CNS) and is the most common cause of long term neurological disability among young adults in Europe and North America (MS Trust, 2015). In MS the body attacks myelin (Figure 1), causing a range of symptoms (see Figure 2). Myelin is the coating which insulates neurons (nerve cells) and helps in the propagation of nerve impulses, which transmit signals from the brain and spinal cord to the rest of our body. There are an estimated 2,500,000 MS cases worldwide and Scotland has the highest rate of MS, with over 11,000 cases. Unfortunately, there is no cure for this devastating disease and the mechanism of the disease is poorly understood.

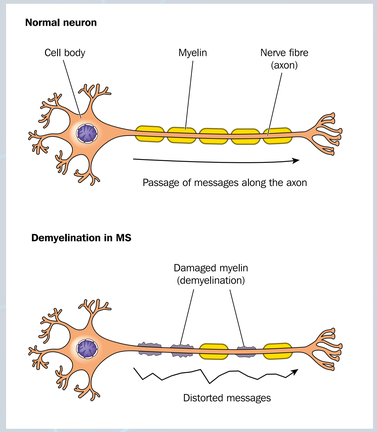

Figure 1 Diagrammatic representation of the defect seen in MS neurons (nerve cells). Reduced covering of myelin slows or stops the transmission of signals along the neurons. Image source: Shutterstock created by Blamb (https://www.shutterstock.com/image-vector/demyelination-multiple-sclerosis-labeled-25484377?src=8sahUOI9NCbJJ5RII_SRxA-1-2).

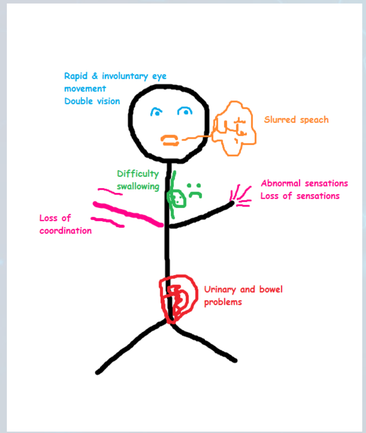

Figure 2 Symptoms seen in MS patients.

What are we interested in?

GM-CSF is a small protein that is produced by immune cells when the body is fighting an infection or is injured. GM-CSF causes the number of cells of our immune system to increase, which is crucial for fighting infections. Mice whose DNA has been altered so they lack GM-CSF are resistant to an animal model of MS, suggesting that GM-CSF may play an important role in MS. We want to study the effects of GM-CSF on the CNS, more precisely on a particular type of cell called microglia, which is a type of immune system cell that lives in the CNS and performs its immune system function by eating up bacteria and cell debris, by a process called phagocytosis. We want to work out how GM-CSF affects microglia and potentially exacerbates tissue damage in the CNS in MS.

What did we do?

To study the effects of GM-CSF on the CNS we used a system similar to the concept of a "brain in a dish". We took cells from the spinal cord of embryonic mice, which contain all the cells present in the CNS, and grew them (cultured them) in the lab. Our cultures develop like in real mice and we can see myelin coating the nerves. We added GM-CSF to the cells and studied the effects using various techniques. For example, we looked at changes in cell appearance using fluorescence microscopy and changes in gene expression using quantitative polymerase chain reaction (PCR).

What did we find?

We found that GM-CSF had no detrimental effect on myelin or the nerve cell axons (see Figure 3), which are the long thin projections of the nerve cells which transmit the nerve impulses (see Figure 1), but we saw a marked response on the microglia. In a resting state, microglia have a branched appearance, but the addition of GM-CSF turned the majority of microglia round and also increased their number (see Figure 4). To investigate what this effect on microglia might mean, we added different materials to the cultures to see whether the microglia's phagocytic capacity is increased in the presence of GM-CSF. Adding GM-CSF to the cultures caused microglia to phagocytose more, regardless of the material we added (see Figure 4).

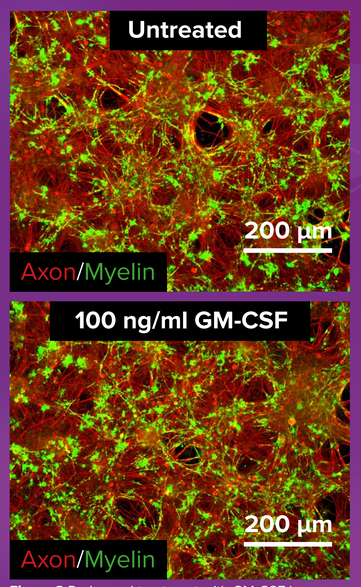

Figure 3 Prolonged treatment with GM-CSF has no detrimental effect on the myelin (green) or axons (red) in our cultures system. (1µm = a thousandth of a mm.)

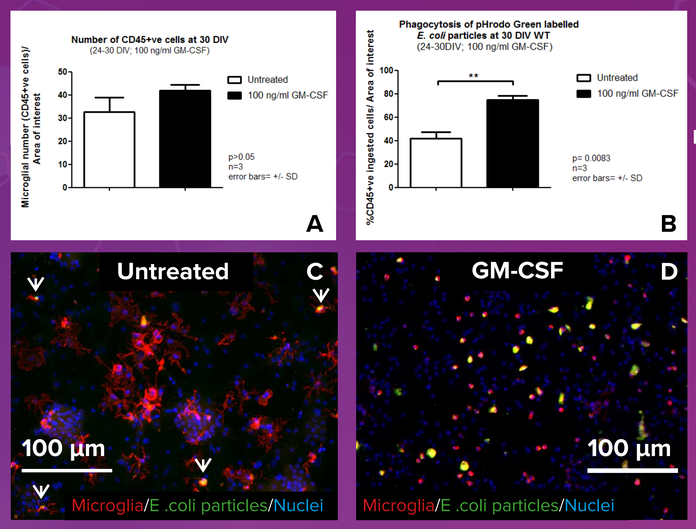

Figure 4 GM-CSF caused an increase in the number of microglia **(A)** and in their phagocytic capacity **(B)**, which ate more *E. coli* bacteria in our culture system. This can be seen by the yellow fluorescent staining of the cells **(D)** which show co-localisation of red labelled microglia and green labelled *E. coli*. Similar results were seen when other test phagocytosis materials we added to the culture system. Note the change of shape of the microglia to a more rounded appearance in the presence of GM-CSF (**(C)** and **(D)**). (1µm = a thousandth of a mm.)

What does this mean?

Our findings suggest that GM-CSF alone is not capable of inducing nerve or myelin damage. On the other hand, we propose that in MS, GM-CSF causes an increase in microglial number which have a higher phagocytic capacity. This means that GM-CSF is equipping microglia for efficient myelin debris clearing. In order to make new myelin to try to restore normal nerve function, the debris has to be removed. This means that GM-CSF appears to be a double edged sword in MS since mice lacking GM-CSF do not get the mouse form of MS, but having GM-CSF helps clear away the myelin debris. This opens new ways of thinking of GM-CSF as a therapeutical target in MS, since having GM-CSF might also be beneficial.

Who am I?

I am currently in the third year of my PhD at the University of Glasgow. I work under the supervision of Professor Chris Linington and Dr Julia Edgar, whose groups focus on the study of neuroinflammation. Before starting my PhD I did my undergraduate degree in Biomedicine at Lancaster University. My PhD is funded by Medical Research Scotland and partly sponsored by a pharmaceutical company, Medimmune Ltd. As a part of my PhD Studentship I have the opportunity to do an industrial placement at Medimmune.

Diana started her PhD project entitled *"Inhibition of GM-CSF signalling cascades in the central nervous system: a new strategy to enhance repair and halt disease progression in multiple sclerosis"* in 2016 and while principally based at the University of Glasgow, supervised by Professor Chris Linington, she is also working closely with Medimmune Ltd.

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