associated with the other velocity component, implying that it condensed from atomic gas *in situ*, rather than being extruded as molecular gas from the inner regions of the SMC itself.

The fate of the gas and stars in the Magellanic bridge is presently unknown. Will it fall back into either of the Magellanic Clouds? Or will it be absorbed into the Milky Way? A third, though more remote, possibility is that the bridge will form a more or less independent system — the Very Small Magellanic Cloud (VSMC). To assess the likelihood of these possibilities, the total mass of the bridge, as well as its kinematics, must be measured and this is best done by observing its atomic and molecular gas components. Should the third scenario indeed be the final outcome (before the Magellanic systems merge with the Milky Way, which is the ultimate outcome), it would mean that a small galaxy has been born right before our eyes.

This would indeed be a remarkable opportunity: one of the outstanding problems in modern astrophysics is to understand how galaxies form. The most successful model of galaxy formation so far has galaxies surrounded by haloes of mysterious, cold dark matter (CDM) — the unseen, 'missing' matter that pervades our Universe; matter as we know it, in the form of stars and gas, is just a small part of the entity that we call a galaxy. In this model, small galaxies form first, dominated by CDM, and are then assembled into larger and larger complexes through gravitational attraction and subsequent merging, following a scheme of so-called hierarchical clustering.

According to the CDM model, in early times our Universe contained relatively large numbers of small galaxies, and this certainly seems to have been the case. The present-day Universe, on the other hand, should contain large galaxies that occasionally grow by 'swallowing' one of the surviving small galaxies. This also seems to be in accordance with observations and the Magellanic system is an example of this process.

But should the Magellanic bridge become free of the LMC and SMC, it would constitute yet another method of galaxy formation. In fact, tidal-debris formation of small galaxies is known to occur in the Universe. Dwarf galaxies formed during violent gravitational interaction between large galaxies —Tidal Dwarf Galaxies, or TDGs — are relatively common, and some of these TDGs are known to contain both stars and molecular gas in a manner similar to the Magellanic bridge[6]. There are even cases where tidally created galactic entities seem to contain only gas, both atomic and molecular, but no stars[7,8]. All of these systems are generally more metal rich and more massive than the Magellanic bridge, but the observations by Muller *et al.*[1] show that the process of tidal galaxy formation seems to be efficient for very small systems as well (even if the Magellanic bridge itself may be a bit too small to become a free galactic entity).

Tidally formed galaxies do not constitute a large population either in numbers or in mass and so will not have any great impact on the future evolution of our Universe. Their ultimate fate is probably to be swallowed by their parent galaxy, or any other large nearby galaxy. Despite their fleeting existence (from a cosmological perspective), they may still be very useful in studies of the structure of the large and extended haloes of their parent galaxies. How TDGs form, their dark-matter composition and their kinematics can tell us how the large parent galaxies themselves formed and how their dark-matter haloes are distributed. Although it is too early to draw conclusions about the CDM haloes from studies of these newly born tidal dwarfs, continued observations may very well reveal something of this elusive dark matter that dominates our Universe. ■

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Medicine

# Tackling multiple sclerosis

Hartmut Wekerle

New work in mice finds that certain anti-cholesterol drugs can reduce symptoms of disease in brain autoimmune disorders that are akin to human multiple sclerosis. There are also hints as to how the drugs might work.

Multiple sclerosis owes its enormous socioeconomic importance to several factors. Worldwide, as many as one million people are affected by the disease. It tends to afflict sufferers for most of their lives, often taking a severe, disabling course. And there are no effective treatments that stop multiple sclerosis in its tracks (although there are some that slow its progression). New therapies are desperately needed, and on page 78 of this issue Youssef and colleagues[1] investigate one attractive candidate — atorvastatin, a drug that is already used to reduce blood cholesterol levels in people with atherosclerosis or heart disease[2].

Multiple sclerosis is generally believed to develop when the body's immune cells — led by so-called helper T cells — attack myelin, the insulating, fatty sheath around nerve cells. This damages the myelin and the underlying neurons in both the brain and the spinal cord (Fig. 1, overleaf), leading to impaired transmission of nerve impulses and progressive physical disability. Treatments available today include one that involves engineered interferon-β proteins, which reduce the inflammation associated with nerve damage. Another is based on copaxone, a random composite of basic peptides, which probably activates brain-protein-detecting T cells that inhibit rather than support the autoimmune attack. Both drugs reduce the number of clinical relapses and the damage to the central nervous system (CNS). But both also come at a price — quite literally in one sense, as they are very expensive. Moreover, they must be administered frequently by injection, which is a severe bother and carries a risk of side-effects. New treatments are needed that can be given orally and that, hopefully, also have a greater effect on the disease.

Enter Youssef *et al.*[1], who have looked at the effects of atorvastatin. This is a member of the statin group of molecules, which are commonly used to treat atherosclerosis and coronary disease[2]. The authors find that the drug is effective against experimental autoimmune encephalomyelitis (EAE), an experimentally induced rodent autoimmune disease that is widely used as a model of human multiple sclerosis. By itself, this finding is perhaps not all that striking. After all, statins have already been used to reduce the rejection of human heart transplants by the immune system, and there have even been reports of a protective effect of injected statins in models of brain autoimmunity similar to EAE[3]. But what is particularly compelling about the new paper is that it provides a clue to the mechanisms by which statins might have anti-inflammatory effects.

Youssef *et al.* used three different models of mouse EAE. These differ in their genetics, the myelin-associated proteins targeted by the immune response, and the resulting 'clinical' diseases — they share basic features, but represent different phases of brain inflammation. After inducing EAE, the authors fed atorvastatin to the animals once a day for

several weeks, and analysed various parameters, such as the amount of CNS damage. They found that the treatment was beneficial in all three models. Moreover, it did not simply prevent the onset of EAE, but also — more importantly for a model of human autoimmunity — reduced established disease.

It seems that statins redirect myelin-specific helper T cells from the destructive role of causing disease to the beneficial task of suppressing autoimmunity. In particular, Youssef *et al.* found that the statins 'reprogramme' a subset of helper T cells (those that express the marker protein CD4). This reprogramming means that the cells no longer produce inflammatory cytokines — messenger molecules — such as interferon-γ and tumour-necrosis factor-β. Instead, they produce anti-inflammatory cytokines, including interleukins 4 and 10 and transforming growth factor-β. In agreement with this, key cytokine-inducing signalling pathways are also redirected in the statin-treated mice. Moreover, when the authors transferred CD4-expressing T cells from treated to untreated mice, those animals also were protected from EAE.

How do statins bring about such changes? These drugs are known to interfere with HMG-CoA reductase, an enzyme needed for cholesterol synthesis, and thus reduce the levels of blood cholesterol. Could such cholesterol reduction also affect the responses of helper T cells? This is a serious possibility, especially given that blood cholesterol modulates the antiviral responses of cytotoxic T cells[4]. But so far it is only known that cholesterol seems to reduce immune activity, so one might expect that statins, which lower cholesterol levels, would stimulate such activity — and that isn't the case in EAE.

The authors seem to favour another, not mutually exclusive, mechanism. They find that atorvastatin inhibits the expression by brain cells of a pivotal regulatory protein, CIITA, which steers the expression of MHC class II molecules. These molecules present peptides (antigens) to helper T cells for recognition. When the peptides are derived from invading microorganisms, the recognition sparks a useful immune response to these pathogens. But when class II molecules present antigens from the body's own cells, this stimulates a harmful autoimmune response such as that seen in multiple sclerosis and EAE.

In this proposed model, then, statins would work through CIITA and MHC class II molecules to decrease the presentation of 'self' antigens, thereby shifting the pattern of helper-T-cell activity. Previous work[5] has shown that statin-mediated reduction in the expression of class II proteins is restricted to those of the body's cells that require a signal from interferon-γ to exhibit these proteins (which ties in nicely with Youssef *et al.*'s results). In contrast, the immune system's 'professional' antigen-presenting cells, such as dendritic cells, would be untouched. This is interesting, but raises questions. According to such a model, statin treatment would not affect dendritic cells in the peripheral immune system — but this is where they are primarily supposed to activate autoimmune T cells. It also remains unknown whether the statin-induced reduction in CIITA expression in the CNS is caused directly by statins, or is an indirect consequence of reduced inflammation.

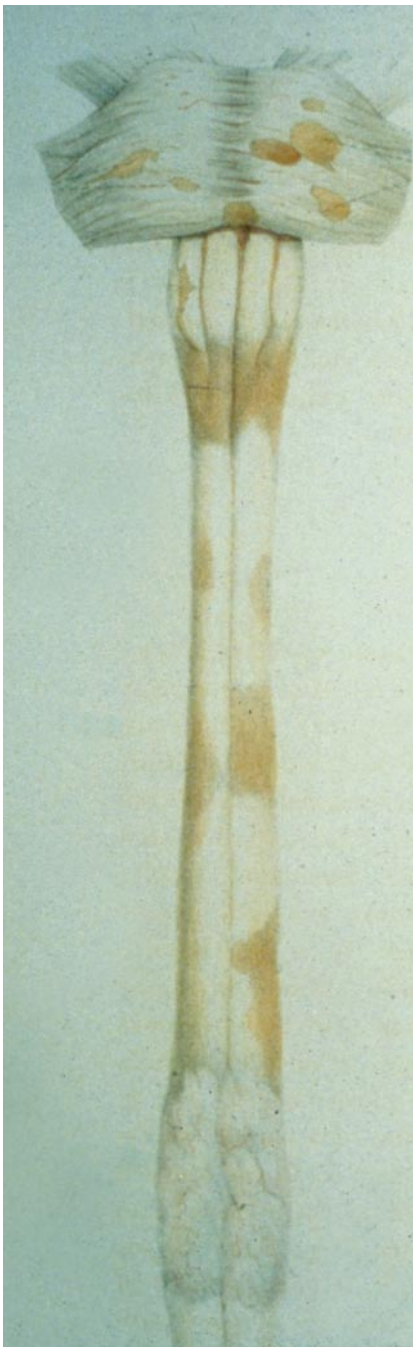

Figure 1 **Brain disease. This lithograph, produced by the nineteenth-century pathologist Jean Cruveilhier[10], is one of the first illustrations of the brain and spinal-cord damage seen in multiple sclerosis. It shows the cerebellum (top) and spinal cord; the randomly distributed dark patches represent damaged areas.**

There is a third possible mechanism. Last year, Weitz-Schmidt *et al.*[6] showed that statins partially block LFA-1, an adhesion molecule involved in T-cell migration and antigen presentation. LFA-1 is a component of the immune synapse — the well-organized site of contact between T cells and antigen-presenting cells. The molecule stabilizes this contact and thus controls the 'strength' of the antigenic signal[7]. Could partial interference with antigen presentation be involved in the T-cell redirection described by Youssef *et al.*? There are many examples in which the strength of antigen recognition by T cells determines the character of the effector molecules produced upon activation. But although this mechanism looks attractive, there are some questions. In particular, it remains to be seen whether EAE is affected by pravastatin, which does not block LFA-1, and by small-molecule LFA-1 blockers that do not inhibit HMG-CoA reductase.

Whatever the mechanism, the data reported by Youssef *et al.*[1] are intriguing, raising hopes of a new, oral treatment for multiple sclerosis and related diseases. But caution is warranted, because none of these three mouse models of EAE develops spontaneously; instead, they are induced by aggressive immunization protocols. So it is hard to use the results of testing potential drugs in these models to predict what will happen in human multiple sclerosis. For instance, interferon-γ aggravates multiple sclerosis, but reduces EAE. The opposite is true[8] of the other main inflammatory cytokine, tumour-necrosis factor-α.

Also, the existing EAE models only represent pathogenesis mediated by CD4-expressing T cells. Emerging data suggest, however, that T cells expressing the other main marker protein, CD8, might also have a role in human multiple sclerosis[9]. This pathogenic pathway might not be affected by statins. But clinical trials of the effects of statins on human multiple sclerosis are now in progress, and could resolve these issues — hopefully in a favourable way. ■

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