New Therapeutic Strategies for Multiple Sclerosis

Remilynto help sustain the health of people afflicted with MS

Introduction

For decades, multiple sclerosis has been explained in terms of autoimmunity and inflammation. Based on these premises, MS patients were given corticosteroids and immunosuppressants with, unfortunately, limited benefits and a range of unwanted side effects. In the search for better drugs, attention was driven to naturally occurring antiviral proteins known as interferons, of which interferon-beta proved to help in lowering the relapse rate and the severity of attacks in MS patients. On another front, the recognition of the pivotal role played by basic myelin protein (BMP) breakdown in triggering autoimmunity in MS led to the development of a cocktail of BMF-derived peptides, known as glatiramer acetate, in the hope to reproduce MS symptoms when injected in animals (Comi and Moiola, 2002). History proved otherwise when glatiramer acetate unexpectedly reduced relapse rate and progression (Arnon, 1996). Glatiramer acetate is now used as an alternative to, interferon-beta in relapsing-remitting MS. Although both interferon-beta and glatiramer acetate are useful in treating MS, they do so for a subset of patients only and do not stop the disease. Moreover, both drugs have the drawbacks of being injectable and quite expensive, leaving room for further therapeutic improvement in MS treatment.

The recent development of new sophisticated non-invasive technologies such as MRI (magnetic resonance imaging) and MRS (magnetic resonance spectroscopy) combined with animal models of the disease have opened a window into MS. Digging deeper in the causes and nature of neuronal damage in MS has allowed the identification of new promising therapeutic targets and strategies.

Saving the Nerves

There is increasing evidence that imbalanced matrix metallo-proteinases (MMPs) activity is involved in MS progression (Yong et al, 2002). Matrix metalloproteinases are a family of zinc-dependent proteases that regulate ECM turnover and also influence important cellular processes through proteolytic processing and shedding of bioactive molecules such as cytokines and growth factors. The suggested roles of MMPs in MS include disruption of the blood-brain barrier, facilitation of immune cell transmigration into the central nervous system and myelin degradation (Sellebjerg and Sorensen, 2003: Yong et al, 2002).

The brain, being a vulnerable and vital organ, is isolated from the nourishing capillaries by a protective shield called the blood brain barrier (BBB). This highly selective barrier consists of a lining of endothelial cells fit so tightly together that no substances can pass freely out of the bloodstream. In the course of MS, repetitive disruption of the BBB paves the way to the subsequent infiltration of activated T lymphocytes and monocytes/macrophages into the central nervous system (CNS). To evade the capillaries and gain access to the CNS these infiltrating lymphocytes and monocytes secrete a variety of MMPs capable of degrading the BBB matrix. Among all known MMP, MMP-9 (a marker of microglia activation) seems to be more specifically involved in BBB breakdown as increased levels of this protease in MS patients is associated with a leaky BRB on magnetic resonance imaging (Rosenberg et al, 1996). Moreover MMP-9 over-expression in MS is predominantly localized around blood vessels in the vicinity of acute lesions and in the active borders of chronic lesions (Anthony et al, 1998).

Besides its contribution to BBB disruption and cellular migration, MMP9 appears also to be involved in the attack on the protective myelin covering of nerve fibers in MS. Indeed, MMP-9 cleaves human myelin basic protein in vitro and this breakdown leads to remnant epitopes that generate autoimmunity (Opdenakker et al, 2001).

Moreover, in an animal model of MS, the injection of highly purified MMPs into the brain resulted in demyelination and axonal loss (Anthony et al, 1996).
Finally, MMPs may contribute to expand the inflammatory response through the conversion of inactive membrane-bound cytokines like TNF-alpha into an active form that is toxic to myelin (Chandler et al., 1997).

Based on these observations, inhibition of MMP-9 activity holds some promise of relief for MS patients. Indeed, when researchers looked at the molecular mechanism underlying the beneficial effects of interferon-beta and steroid treatments in MS, they noticed that both significantly inhibit MMP-9 enzymatic activity and protein expression level in vitro (Ma et al., 2001), and normalize serum MMP-9 activity level in relapsing-remitting MS patients (Trojano et at, 1999). MMP-9 inhibition in these studies correlate with a reduction in BBB breakdown, lymphocyte migration, inflammation and demyelination (Stuve et al., 1996).

In addition to MMP activation, inflammatory processes as seen in MS are known to trigger the release of a vascular growth factor (VEGF). VEGF is like an emergency switch driving the formation of new blood vessels to help healing wounds. An important and distinctive characteristic of these new blood vessels is their leakiness which is essential for their normal healing functions and allows immune cells and repairing proteins to accumulate at the site of wound. These new blood vessels normally resorb quickly once the healing process has been completed. Nevertheless, in some pathological situations like MS, they persist, contributing to sustain an inflammatory process.

An additional relationship between VEGF expression and MS was recently described. Using immunohistochemistry and molecular biology, VEGF overexpression was detected in acute and chronic MS plaques (Proescholdt et al, 2002). It is suspected that the increased blood vessel permeability induced by VEGF in MS contribute to the leak of fibrinogen from the blood into the damaged nerve. Fibrinogen is a plasma protein that normally helps to form blood clots. In the vicinity of a nerve, it is possible that fibrinogen might be proteolyzed into fibrin by MMPs (Gveric et al. 2001). Fibrin is found in MS lesions where its presence prevents Schwann cells from beginning their repair job (Akassoglou et al., 2002). Schwann cells are involved in regenerating the myelin sheath.

**Undoing the Damage to Myelin**

Until very recently, talking about nerve regeneration would have appeared as a heresy. The scientific dogma held that once myelin was lost in the CNS, it was lost forever. Thanks to some unconventional researchers and to the strength of a Superman (Christopher Reeve), we now know this to be untrue. The CNS can, to a certain point, regenerate itself. It can remyelinate from cells within the CNS that are still capable of forming new myelin, and it can remyelinate from stem cells which are immature cells that can differentiate into myelin-making cells (Johansson, 2003; Korbling and Estrov, 2003). The problem in MS seems to be that myelin loss proceeds more aggressively and quickly than remyelination. Identifying all the factors at play in the balance of nerve maintenance will surely one day revolutionize the therapeutic approach to nerve injury.

Meanwhile, studies done with animal models point to signaling factors called growth or "trophic" factors as potential mediators of nerve cell repair. CNTF (Ciliary Neurotrophic Factor), leukemia inhibitory factor (LIF), cardiotrophin-1, and oncostatin M, are among the factors shown to induce a strong promyelinating effect (Stankoff et al. 2002). CNTF is a survival factor for neurons that promote differentiation, maturation, and survival of oligodendrocytes. When CNTF-deficient mice were used in an animal model of MS, disease was more severe and recovery was poorer (Linker at al, 2002). Involvement of CNTF in nerve healing is further supported by another animal study showing that astrocytes in the CNS produce increased amounts of CNTF during the remyelination phase (Albrecht et al. 2003). CNTF appears to contribute to remyelination at least partly through stimulation of FGF-2 (fibroblast growth factor) production. Interestingly, glatiramer acetate (one of the current drugs used in MS) was reported to stimulate the production of some neurotrophic factors reinforcing the potential of such signaling factors as tools in MS therapies (Ziemssen at al, 2002).

**Conclusion**

It is an exciting time for MS research. Our view of the mechanisms at stake in the progression of the disease is becoming clearer and new strategies are being developed for MS treatment. Inhibition of MMP activity to stop disease progression and the use of stem cells and neurotrophic factors with their regenerating power are emerging as promising new avenues in the care of MS patients.

In light of the accumulating knowledge around MS causes and mechanisms, Atrium Biotechnologies has formulated a new product called Remilyn to help sustain the health of people afflicted with MS. Remilyn has proven anti-MMF and anti-VEGF activities and is enriched with signaling factors usually found in stem cells and nerve cells.