Could a vaccine treat spinal cord injury?

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Damage to the CNS causes the body to mount an immune reaction against itself that protects neurons from further damage[1]. This has been shown for the first time by scientists from The Weizmann Institute of Science (Rehovot, Israel) and could have implications for the development of vaccines to improve functional recovery following spinal cord injury.

Immune activity: good or bad?

'Up until a couple of years ago the general wisdom was that any immune activity was bad for the CNS. But our findings have led us to believe that some immune activity is needed for CNS homeostasis and repair, and that it can be of benefit if you keep it tightly controlled,' says Michal Schwartz, Professor of Neuroimmunology in the Department of Neurobiology at the Weizmann Institute.

The role of the immune system in the post-traumatic spread of damage has been a subject of controversy. Anti-inflammatory compounds, such as methylprednisolone[2], dexamethasone[3] and certain cytokines[4] that are known to suppress the immune response, have been found to restrict the spread of damage at an early post-traumatic stage, and yet macrophages were shown to be needed for regrowth of injured nerves[5].

Another conflicting finding is the effect observed in rats with crush-injured optic nerves or contused spinal cords after treatment with interleukin-10 (IL-10). Shortly after injury there appears to be neuronal benefit, whereas if treatment is later, the effect appears to be destructive[6].

Despite intensive research in the field of neuroprotection, including some Phase III studies, no immune-modulating drugs have been approved for clinical use.

In an earlier study, Schwartz and colleagues found that if they passively transferred T cells specific to CNS myelin ('autoimmune' T cells) into a rat with an injured optic nerve, recovery (assessed as the number of surviving neurons and the restoration of motor ability) was better than in rats that had received no such transfer[7–9].

Mechanism of neuroprotection

'Those results raised the question of whether the observed neuroprotection was a physiological phenomenon or was just the result of an experimental manipulation,' says Schwartz. To answer this question, Schwartz and her team undertook four different experimental paradigms in rodents[1].

In the first experiment, they examined whether the outcome of an injury to the optic nerve was better or worse if preceded by an injury at a different CNS site (the spinal cord) and investigated the optimal time interval between the two injuries. They found that a beneficial effect could be observed if the injury occurred at any time between 7 and 17 days. 'But what this didn't tell us was whether the benefits were induced by hormones, cytokines or antibodies,' says Schwartz.

The next paradigm was designed to produce more specific results. They showed that spleen cells transferred from spinally injured rats to newly injured rats provided a neuroprotective effect. 'This proved to us that the systemic beneficial effect evoked by the spinal cord injury is mediated by immune cells and not by antibodies or other immune-associated soluble factors,' says Schwartz.

In the third paradigm they found that the outcome of crush injury to the rat optic nerve, with or without previous damage to the spinal cord, was worse in rats in which the thymus glands had been removed at birth. Because this gland is responsible for manufacturing T cells, this experiment demonstrated that the autoimmune response observed is a beneficial physiological phenomenon mediated by T cells.

Next, the group compared the effect of optic-nerve injury in transgenic mice that over-express T-cell receptors for myelin basic protein (MBP) and some regulatory T cells, with mice that over-express T-cell receptors for ovalbumin, a peptide that is not found in mice. The finding that endogenous neuroprotection occurred only in the first group showed that antigen specificity is crucial for the observed neuroprotection, and that not all T cells can do the job.

Taken together, these four independent experiments show that CNS trauma spontaneously evokes a beneficial T-cell-dependent autoimmune response that reduces neuronal loss. These findings could provide an explanation for the frequent observation that T cells directed to self-antigens (such as MBP) are present in healthy individuals. One possible mechanism of action is that T cells could be activating or regulating microglia (the CNS equivalent of macrophages) to exert a beneficial effect.

Vaccine for neurodegenerative disorders?

The results of this research raise the possibility that the body's own physiological response to injury can be boosted for therapeutic purposes using vaccination to raise the beneficial T-cell count. This procedure could be helpful in treating neurodegenerative conditions such as spinal cord injury, head injury, glaucoma, Parkinson's disease, Alzheimer's disease and others.

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'Given the restricted therapeutic window after injury, and the fact that the effect is T-cell mediated, we thought that active vaccination (which induces speedy production of T cells) would be quicker than raising T cells *in vitro* and then injecting them into the body,' says Eti Yoles, formerly a research associate in Schwartz's laboratory at the Weizmann Institute, and now Vice-President of Research at Proneuron (Rehovot, Israel; a biotechnology company that is developing the vaccine).

For its animal studies the team is currently using rats and mice with spinal cord and optic nerve injuries to compare the effects of vaccination either with Copaxone (glatiramer acetate) or non-pathogenic synthetic derivatives of peptides derived from myelin antigens. Copaxone is a synthetic copolymer consisting of four amino-acids (alanine, lysine, tyrosine and glutamate), which has already been approved by the FDA as being safe and having no adverse side-effects. It is hoped that T cells that react against Copaxone will also work against MBP.

Clinical trials are planned in which patients with glaucoma or spinal cord injury will be vaccinated with either Copaxone or with modified peptides in an attempt to prevent the progressive loss of retinal ganglion cells. 'Because we are dealing with the body's own mechanism of repair, we hope the vaccine will cause fewer safety problems', says Schwartz.

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New hope for sickle cell anaemia

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Two recent studies have suggested new approaches to the treatment of sickle cell anaemia. Robert Iannone and colleagues (Johns Hopkins Hospital and Oncology Center, Baltimore, MD, USA) have developed a chimaeric stem-cell transplant technique[1] in mice that might reduce anaemia in those with sickle-cell disease (SCD), while minimizing the risk of a traditional bone-marrow transplant. More fundamental research by Leslie Parise's group at the University of North Carolina (Chapel Hill, NC, USA) has identified a novel synergy between the signalling of integrin-associated protein (IAP) and shear stress, which might explain why sickled erythrocytes adhere to the inner wall of blood vessels[2]. Blocking this pathway could be a future strategy for preventing the vaso-occlusive crises and degenerative organ damage that is typical of SCD.

A 'mini-transplant': getting the correct balance

Conventional bone-marrow transplantation is the only therapy for SCD that has curative potential but it carries the risks of disease recurrence, long-term adverse effects caused by transplant conditioning or graft-versus-host disease, and death. However, SCD patients who have serendipitously developed mixed chimaerism, after their own bone marrow has been only partially ablated, remain symptom free and have a much lower complication rate. These observations led Iannone and colleagues to use a mouse model to investigate the 'optimum' balance between self and donor cells after a bone marrow transplant, and to examine whether a chimaeric transplant resulted in increased organ pathology. Lethally irradiated mice were given varying rations of T-cell depleted marrow from normal and transgenic 'sickle-cell' mice, producing different ratios of myeloid chimaerism. Mice that had 25:75% normal:sickle stem-cells had >90% normal haemoglobin in their blood, but this was insufficient to reduce

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