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Protective autoimmunity in neurodegenerative and mental disorders

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Acute or chronic damage to the central nervous system (CNS) triggers self-perpetuating 'secondary degeneration', caused by cytotoxic mediators (neurotransmitters, free radicals) emanating from lesioned sites. Local and infiltrating anti-self immune cells at the injury site were long considered pathological. Our findings suggested, however that autoimmunity is a beneficial fighting force against destructive self-derived compounds, leading us to redefine 'tolerance to self', long equated with 'nonresponsiveness', as ability to tolerate autoimmune responses without developing an autoimmune disease. We thus perceive autoimmunity as a physiological repair mechanism possessing the on/off switch needed to maintain or restore tissue homeostasis without attendant autoimmune disease, and controlled by naturally occurring CD4+CD25+ regulatory T cells (Treg), themselves controlled by brain-derived neurotransmitters/peptides. If ongoing neurodegeneration after acute injuries results from insufficiency of the endogenous fighting force, and chronic neurodegenerative diseases reflect age-related deterioration of the body's two principal regulators (CNS and immune system), restoration or boosting of immune function might bridge the gap between manifestation of CNS-related risk factors and the immune system's defensive capacity. Boosting of peripheral immunity, by vaccinating with a universal weak anti-T-cell antigen or its agonist, or by weakening suppression of autoimmunity (e.g., by eliminating Treg), might be developed as therapies to counteract multiple risk factors. T cells that home to the damaged CNS might then help restore homeostasis there by regulating glial behavior and producing neurotrophic factors, while avoiding cytotoxic inflammatory activity. Since neurodegenerative diseases possess some common features deriving from the local chaos, the same vaccine might protect against

several disorders associated with impairment of brain function (motor, cognitive and mental).

Selected Publications

- Rapalino et al. (1998) Implantation of stimulated macrophages leads to partial recovery of paraplegic rats. *Nat. Med.* 4:814-821.
- Moalem et al. (1999) Autoimmune T cells limit secondary degeneration following central nervous system trauma. *Nat. Med.* 5:49-65.
- Hauben et al. (2000) Autoimmune T cells are neuroprotective in Spinal cord injury. *Lancet.* 355: 286-287.
- Kipnis et al (2000) Immunization with copolymer-1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. *Proc. Natl. Acad. Sci. (USA)* 97:7446-7451.
- Moalem et al (2000) Production of neurotrophins by activated T cells: implications for neuroprotective autoimmunity. *J. Autoimmunity* 15: 331-345.
- Schori et al (2001) Vaccination for protection of neurons against glutamate cytotoxicity and ocular hypertension: implications for glaucoma. *Proc. Natl. Acad. Sci. (USA)* 13:3398-403.
- Kipnis et al (2001) Genetic control of immune response to trauma: vaccination for acute and chronic CNS degenerative disorders. *J. Neurosci.* 21:4564-4571.
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- Hauben et al (2001) Post-traumatic immunization for spinal cord recovery: benefit without risk of pathogenicity. *J Clin Invest.* 108: 591-599
- Mizrahi et al. (2002) The tissue-specific self-pathogen is the protective self-antigen: The case of uveitis. *J. Immunol.* 169:5971-5977.
- Kipnis et al.(2002) Neuroprotective autoimmunity: Naturally occurring CD4+CD25+ regulatory T cells suppress the ability to withstand injury to the central

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- Kipnis, J. and Schwartz, M. (2002) Dual action of glatiramer acetate (Cop-1) in the treatment of CNS autoimmune and neurodegenerative disorders. *Trends Mol. Med.* 8:319-323.
- Schwartz, M. and Kipnis, J. (2002) Multiple sclerosis as a by-product of the failure to sustain protective autoimmunity: A paradigm shift. *The Neuroscientist*, 8:405-13.
- Schwartz, M., Shaked, I., Fisher, J., Mizrahi, T. and Schori, H. (2003) Protective autoimmunity against the enemy within: Fighting glutamate toxicity. *Trends Neurosci.* 26: 297-302.
- Hauben, E. and Schwartz, M. (2003) Therapeutic vaccination for spinal cord injury: Helping the body to cure itself. *Trends Pharmacol.* 24:7-12.
- Kipnis et al. (2004) T cell deficiency leads to cognitive dysfunction: Implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. *Proc. Natl. Acad. Sci. USA.* (101(21); 8180-8185)
- Schwartz, M. and Kipnis, J. (2004) A common vaccine for fighting off neurodegenerative disorders: recharging immunity for homeostasis. *Trends Pharmacol.* (In press).