Autoimmunity and adult stem cells in CNS maintenance and repair: Implications for acute injuries, neurodegenerative diseases, and mental dysfunction

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The immune system is known to be important for defense against external intruders. The possibility that immune cells also protect the body from destructive self-compounds ('the enemy within') was demonstrated by our group 7 years ago. We found that autoimmune T cells specific to central nervous system (CNS) autoantigens play a neuroprotective role following an injury to the CNS (Moalem et al., 1999). This phenomenon, which we termed 'protective autoimmunity', implies that there is a distinction between autoimmunity and autoimmune disease; the former is a purposeful response needed to fight off adverse conditions (whatever their primary cause) that result from tissue damage, whereas the latter occurs when this purposeful response is out of control. According to this view, specificity to autoantigens does not imply an attack on tissues expressing these self-proteins; rather, such specificity ensures homing of T cells to sites of injury. We have established that CNS-specific T cells, provided that their activity is well controlled, interact with CNS-resident microglia to the benefit of the injured CNS (Schwartz et al., 2003). Thus, for example, immunization with myelin-associated antigens confers neuroprotection and functional recovery after contusive spinal cord injury (Hauben et al., 2001; Hauben et al., 2000).

In the recent years our group has focused on the interaction between the immune system and the nervous system in the context of adult neural stem cells. Our group has shown that microglia, when activated by the immune system's adaptive arm (represented by T cells or T-cell derived cytokines), acquire a phenotype which, via production of growth factors such as insulin-like growth factor (IGF-I) and growth-promoting cytokines, supports neuronal survival (Butovsky et al., 2005; Shaked et al., 2005) and induces adult neural stem/progenitor cell to differentiate into neurons and oligodendrocytes (myelin-forming cells)(Butovsky et al., 2006b). Using an animal model of multiple sclerosis, we have demonstrated that administration of microglia pretreated with T-cell derived cytokines can ameliorate neurological deficits and induce the formation of new oligodendrocytes from endogenous stem/progenitor cells (Butovsky et al., 2006a). In addition, we found that boosting the CNS-specific T-cell response with transplantation of adult neural progenitor cells synergistically promotes functional recovery after spinal cord injury. In the course of our studies we have identified additional components that can beneficially affect microglial response at the injured sites. Among such elements are the extracellular matrix protein Chondroitin sulphate proteoglycan (CSPG) and its disaccharide degrading product (CSPG-DS) (Rolls et al., 2004; Rolls et al., 2006).

Recently, we extended our understanding of the role of the dialogue between resident microglia and T cells recognizing CNS autoantigens to include maintenance of healthy brain plasticity (Cohen et al., 2006; Kipnis et al., 2004; Ziv et al., 2006). Neurogenesis, the formation of new neurons from stem/progenitor cells, occurs constantly in a few selected areas of the adult brain, and is considered to be important for certain cognitive functions. We found that in immune-deficient mice (SCID or nude), as well as in transgenic mice in which the majority of T cells specifically recognize a CNS-irrelevant antigen (ovalbumin), both adult hippocampal neurogenesis and spatial learning abilities are impaired. We also discovered that specific recognition of CNS autoantigens by T cells is needed for the

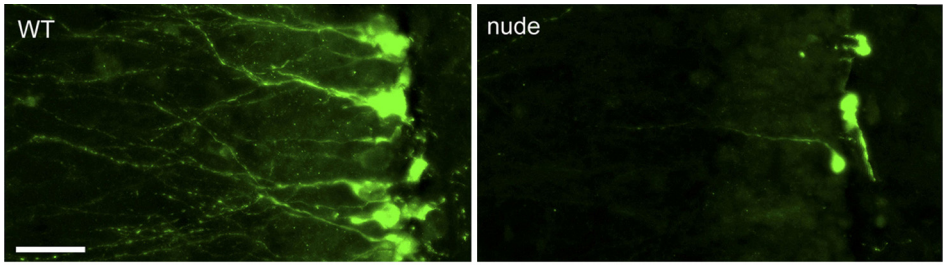

Fig. 1 *Staining for the early neuronal differentiation marker DCX in the dentate gyrus reveals significantly less newly formed neurons and shorter dendrites in nude mice (right panel) than in the wild type (left panel).*

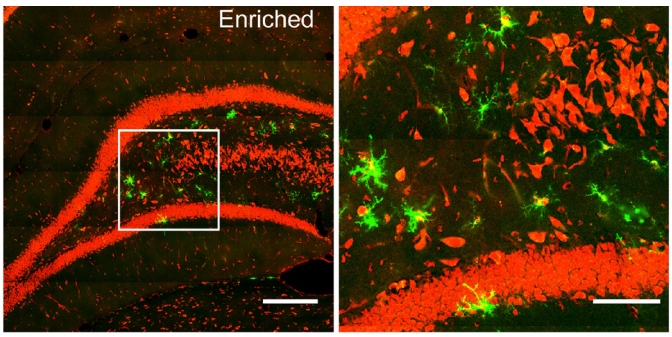

Fig. 2 *Microglia expressing MHC-II (green) appear in the hippocampal neurogenic site of rats housed in enriched environment.*

maintenance of adult neurogenesis and spatial learning abilities. These findings led us to suggest that the primary role of T cells recognizing autoantigens is maintenance of the healthy CNS, and that their role under pathological conditions is an extension of this primary function.

Current work in our laboratory is aimed at determining the exact mechanisms by which peripheral adaptive immune cells (T cells and B cells) interact with CNS-resident innate immune cells (microglia). We are also seeking optimal antigens for the purpose of developing a T cell-based vaccination to slow down brain senescence and fight off neurodegenerative diseases associated with cognitive loss (such as Alzheimer disease), motor disability (ALS), and mental distress (depression). In addition, the identification of T cells and microglia as key players in maintaining neurogenesis at adulthood has prompted us to develop a novel approach of a combination therapy of autologous adult stem cells and T-cell based vaccination for fatal neurodegenerative CNS conditions.

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