Immunity to self and self-maintenance: a unified theory of brain function and dysfunction

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Previous studies by our lab have shown that immune cells contribute to neuronal survival following central nervous system (CNS) injury. This neuroprotective effect was found to be mediated primarily by T cells that recognize self-antigens associated with the injured site, and by myeloid cells such as macrophages and microglia. These findings point to a distinction between 'protective autoimmunity' – a naturally occurring physiological mechanism for damage restriction, and 'autoimmune disease' – a condition of uncontrolled and detrimental autoimmune activity. Recently we have elaborated on the concept of protective autoimmunity, and showed that immune cells are not only involved in neuroprotection following injury, but are also crucially important for maintaining the functional integrity of the brain under normal non-pathological conditions. At the molecular and cellular levels we found that CNS-specific T cells and bone marrow derived myeloid cells (e.g. dendritic cells and macrophages) support a multitude of processes for maintaining plasticity in the healthy adult brain (such as the generation of new neurons from stem and progenitor cells and the regulation of neurotrophic factors expression). At the behavioral level we found that deficiency in CNS-specific T cells results in impaired hippocampus-dependent cognitive abilities and reduced resilience to psychological stress. Currently, our lab is focused on elucidating the mechanisms that underlie the activity of the immune system as a central maintenance and repair apparatus of the CNS. Our working hypothesis is that the loss or deficiency of immunity to certain self-antigens, or its insufficiency when encountering increased levels of risk factors, is an important underlying factor in the onset or escalation of various degenerative processes in the CNS. Using animal models of acute CNS insult (such as spinal cord injury and stroke), and chronic neurodegenerative disease (such as Alzheimer and amyotrophic lateral sclerosis), mental dysfunction (such as acute stress or chronic depression), and age-related cognitive loss we have been able to show that specific manipulation of immune activity can promote functional recovery from acute insults, slow down deterioration under chronic diseases, and promote cell renewal.

Under 'Normal conditions', the choroid plexus, the meninges and the perivascular spaces (collectively referred to as the 'Borders of the CNS') harbor bone marrow derived macrophages and dendritic cells, which constantly express low levels of MHC-II. CNS-specific memory T cells can cross the blood-brain barrier or the blood-CSF barrier at the choroid plexus and interact with dendritic cells at the borders of the CNS. Following this interaction, cytokines and growth factors produced by the macrophages or dendritic cells and the T cells, can affect cells at the brain parenchyma. Growth factors such as IGF-1 can influence cell renewal from endogenous stem and progenitor cells and positively regulate the neuronal production of BDNF. Additionally, T cell derived cytokines, such as IL-4, can induce local production of IGF-1 in the brain parenchyma by resident microglia. Enhanced activity can lead to an enhanced antigen drainage to the cervical lymph nodes and to a subsequent egress of CNS-specific T cells to the circulation. Under 'pathological conditions', (e.g ischemic stroke, or spinal cord injury) immune activity is shifted to the parenchyma itself (due to transient opening of the BBB and robust damage-induced activation of resident microglia), while antigen drainage, and immune-cell mobilization from the lymph nodes and bone marrow are enhanced. Interactions between T cells and microglia at the injured parenchyma contribute to the recruitment of blood-borne monocytes, which locally differentiate into macrophages and dendritic cells that are able to produce growth factors, such as IGF-I and BDNF. These immune responses also act to mobilize stem and progenitor cells from their niches. Upon their arrival to the lesion site, stem and progenitor cells serve a dual role by contributing to cell renewal, and to local immune modulation via a cross talk with resident immune cells.

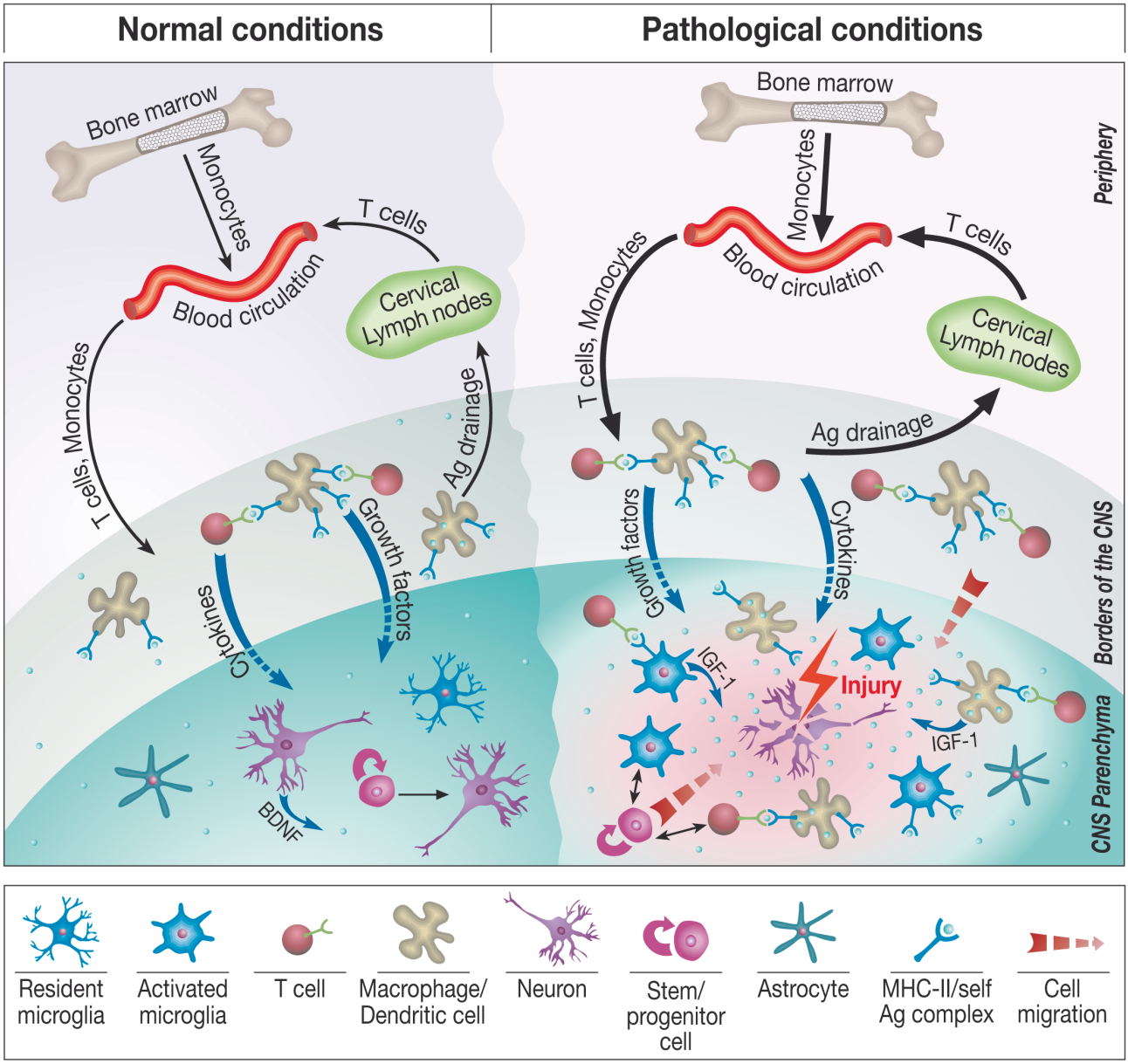

Fig. 1 *Under 'Normal conditions', the choroid plexus, the meninges and the perivascular spaces (collectively referred to as the 'Borders of the CNS') harbor bone marrow derived macrophages and dendritic cells, which constantly express low levels of MHC-II. CNS-specific memory T cells can cross the blood-brain barrier or the blood-CSF barrier at the choroid plexus and interact with dendritic cells at the borders of the CNS. Following this interaction, cytokines and growth factors produced by the macrophages or dendritic cells and the T cells, can affect cells at the brain parenchyma. Growth factors such as IGF-1 can influence cell renewal from endogenous stem and progenitor cells and positively regulate the neuronal production of BDNF. Additionally, T cell derived cytokines, such as IL-4, can induce local production of IGF-1 in the brain parenchyma by resident microglia. Enhanced activity can lead to an enhanced antigen drainage to the cervical lymph nodes and to a subsequent egress of CNS-specific T cells to the circulation. Under 'pathological conditions', (e.g ischemic stroke, or spinal cord injury) immune activity is shifted to the parenchyma itself (due to transient opening of the BBB and robust damage-induced activation of resident microglia), while antigen drainage, and immune-cell mobilization from the lymph nodes and bone marrow are enhanced. Interactions between T cells and microglia at the injured parenchyma contribute to the recruitment of blood-borne monocytes, which locally differentiate into macrophages and dendritic cells that are able to produce growth factors, such as IGF-I and BDNF. These immune responses also act to mobilize stem and progenitor cells from their niches. Upon their arrival to the lesion site, stem and progenitor cells serve a dual role by contributing to cell renewal, and to local immune modulation via a cross talk with resident immune cells.*

Selected Publications

Butovsky, O., Koronyo-Hamaoui, M., Kunis, G., Ophir, E., Landa, G., Cohen, H. and Schwartz, M. (2006a) Glatiramer acetate fights against Alzheimer's disease by inducing dendritic-like microglia expressing insulin-like growth factor 1. *Proc Natl Acad Sci U S A*, 103, 11784-11789.

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