**HYPOTHESIS**

**Can immunotherapy treat neurodegeneration?**

Cancer immunotherapy could guide treatment for Alzheimer's disease

By Michal Schwartz

Alzheimer's disease (AD) is a devastating age-related neurodegenerative disorder and the most frequent cause of senile dementia. The appearance of cognitive decline in this disease is associated with synaptic and neuronal loss, intracellular neurofibrillary tangles, the accumulation of intracellular and extracellular plaques of misfolded amyloid-β (Aβ) peptide, and local neuroinflammation. The major focus in AD therapeutics has been to directly target specific factors in the brain that are believed to be associated with pathogenesis—primarily Aβ and tau proteins—by using immunological or pharmacological tools. However, in the clinic, these therapies have not shown efficacy in restoring cognitive function nor in arresting the disease course. In addition, treating brain inflammation, which often accompanies neurodegenerative diseases, with nonsteroidal anti-inflammatory drugs has shown limited or no effect on disease progression (1). Collectively, these results have led investigators to revisit the identification of the factors participating in AD and in particular the role of the immune system, including the resident brain myeloid cells (microglia) and the innate and adaptive arms of the immune system.

**BRAIN-IMMUNE DIALOGUE**

Until recently, the brain was considered exempt from systemic immune surveillance, the process by which immune cells patrol tissues and organs, providing tissue maintenance and defense. However, we now know that there is an ongoing, lifelong dialogue between the brain and the immune system in which circulating immune cells have an indispensable role in brain tissue maintenance and repair (2–5). Specifically, cellular components of the systemic immune system affect physiological brain function and plasticity (2, 5) and promote tissue repair in the central nervous system (CNS) after injury (3, 4). Although microglia are the primary mediators of immune surveillance in the healthy brain, under pathological conditions the infiltrating blood-borne monocytes display an important, distinct, and nonredundant role in controlling neuropathological events in the CNS (4). Notably, blood-borne myeloid cells that enter the CNS can contribute to numerous aspects of tissue repair, including resolution of inflammation, scar degradation, and neurotrophic factor production.

The finding that circulating immune cells contribute to brain plasticity prompted studies investigating where and how such brain-immune dialogue takes place. This has shifted much of the research focus to the borders of the CNS. These borders encompass several different anatomical structures, each engaged in different relationships with the immune system. The blood-brain barrier—an absolute barrier that is essential for the proper function of the CNS—is formed by tightly connected endothelial cells that are surrounded by basal lamina and astrocyte endfeet. Other barriers include the meninges, which provide the CNS with lymphatic vasculature (6), and the blood-cerebrospinal barrier (B-CSF-B); both act as immunological interfaces rather than simply as inert barricades (5).

Thus, for example, one of the essential activities of the B-CSF-B, mediated through its epithelial choroid plexus layer, is to provide a gateway for transepithelial migration of monocytes (5). The activity of this gateway depends on the availability of systemic T cell–derived interferon-γ (IFN-γ).

Both innate and adaptive immunity modify AD onset and progression. Accordingly, boosting recruitment of monocyte-derived macrophages to sites of brain pathology in AD animal models is effective in arresting disease (7, 8). Moreover, AD severity is greater in immunocompromised mice (9). These findings, together with the observed dysfunction of the brain's choroid plexus in animal models of aging and AD (10–12), suggest that the diseased brain escapes from immune surveillance, at least in part, because of decreased cell entry through the choroid plexus. Collectively, such observations suggest an alternative view of leukocyte entry into the brain—rather than invaders that should always be blocked, these cells have the potential to be beneficial, and under certain conditions should be recruited, engaged, and activated.

**A LESSON FROM CANCER IMMUNOTHERAPY**

A transition from viewing the immune system as an enemy that should be suppressed, to a new view of increasing selective recruitment of immune cells to fight brain pathologies has spurred the search for therapies that harness the immune system to combat disease, rather than therapies that target disease-escalating factors in the brain. This transition is reminiscent of the revolution in cancer therapy in which strategies have shifted from targeting the tumor to harnessing the immune system to eradicate the malignancy.

For decades, cancer therapy has focused on drugs that kill the tumor itself, often with limited success. However, with the growing recognition that the body's immune surveillance system recognizes and eradicates cancerous cells before a tumor develops, and that malignant cells escape from immune control, research has shifted to searching for immunotherapies to overcome such escape mechanisms. Among the tumor escape mechanisms that have been attractive targets for immune therapies are regulatory T cells that dampen the immune response, and the expression of inhibitory immune checkpoint ligands by the tumor, which inhibit immune cells possessing antitumor activity. Recent efforts have focused on developing therapies to block inhibitory immune checkpoint activity, such as antibodies directed against the programmed cell death 1 (PD-1)/PD-L1 pathway (13). This approach facilitates mobilization of immune cells to tumor sites and overcomes local mechanisms that interfere with their activity (13).

The concept of mobilizing the immune system to fight tumors dates back to German physician Rudolf Virchow in the mid-19th century and to the attempts of American physician William Coley at the end of the 19th century to treat tumors by using injections of bacteria to evoke a strong immune response. However, implementation of this approach was delayed. In the mid-20th century, the notion of using immunotherapy to treat cancer was revived on the basis of the theory of cancer immunosurveillance, which suggests that lymphocytes act as sentinels...
that identify and eliminate somatic cells transformed through spontaneous mutations. The absence of data supporting the existence of tumor-specific antigens delayed progress in this area for some time. Therefore, immunotherapy for cancer has only reached fruition in recent years.

In analogy to cancer, well-controlled mobilization of immune cells (leukocytes) to the diseased brain could be considered a potential means to overcome immune escape mechanisms and could serve as a strategy to modify the course of AD. Approaches taken to increase leukocyte recruitment include directly augmenting circulating monocytes so as to consequently increase the number of monocyte-derived macrophages in the brain (7, 8); transiently reducing the number of immune suppressor T cells (those expressing the transcription regulatory factor called forkhead box P3 (FoxP3)) in the periphery (11); and transiently blocking inhibitory immune checkpoints (by using antibody to PD-1 (14), which in turn allows recruitment of disease-modifying leukocytes to sites of brain pathology. Immune cells that infiltrate the CNS parenchyma in AD follow a chemokine gradient and home to sites of brain pathology, where they can support or participate in numerous reparative activities, including phagocytosis of cell debris and amyloid plaques, modification of the inflammatory milieu, and degradation of the glial scar, which could ultimately lead to neuroprotection (see the figure) (14).

Although the suboptimal immunosurveillance observed in the context of AD could be a functional outcome of insufficient leukocyte trafficking to the CNS, it might be primarily due to inadequate surveillance by resident microglia within the brain. The reasons why microglia fail to eradicate pathological factors in CNS remain a subject of debate. It is possible, as is the case for systemic immunity, that the mechanisms that keep microglia under strict control (which could be viewed as microglial checkpoints) are optimized for function under normal physiology. Such mechanisms allow microglia to eradicate threats under physiological conditions without endangering neighboring cells in the brain, but might become disadvantageous when a strong phagocytic response is required, as in AD. This contention may be supported by the fact that the expression of microglial checkpoints, such as the C-X-C motif chemokine receptor (CX3CR1; known as the fractalkine receptor), is spontaneously down-regulated as an interim step in the activation of microglia toward their full phagocytic activity (15). Moreover, in animal models of AD, when CX3CR1 expression is inhibited, the disease severity is reduced.

**A model of AD therapy**

In AD, like cancer, disease progression is associated with systemic immunosuppression.

**Lymph nodes**

Upon systemic PD-1 blockade with antibody, immune cells mobilize. TCR, T cell receptor; MHC, major histocompatibility complex; APC, antigen-presenting cell.

**B-CSF-B**

Leukocyte entry into the CNS is controlled by IFN-γ-dependent choroid plexus responses.

**CNS parenchyma**

Infiltrating immune cells help to clear toxic proteins, resolve inflammation, rescue neurons, and mitigate cognitive defects.

**REFERENCES AND NOTES**

16. See supplementary materials for additional references.

**SUPPLEMENTARY MATERIALS**

www.sciencemag.org/content/357/6348/254/suppl/DC1

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