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*J Immunol* 2020; 204:243-250; doi: 10.4049/jimmunol.1900844

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A 20-Year Journey from Axonal Injury to Neurodegenerative Diseases and the Prospect of Immunotheraphy for Combating Alzheimer’s Disease

Michal Schwartz,*† Javier M. Peralta Ramos,† and Hila Ben-Yehuda†

The understanding of the dialogue between the brain and the immune system has undergone dramatic changes over the last two decades, with immense impact on the perception of neurodegenerative diseases, mental dysfunction, and many other brain pathologic conditions. Accumulated results have suggested that optimal function of the brain is dependent on support from the immune system, provided that this immune response is tightly controlled. Moreover, in contrast to the previous prevailing dogma, it is now widely accepted that circulating immune cells are needed for coping with brain pathologies and that their optimal effect is dependent on their type, location, and activity. In this perspective, we describe our own scientific journey, reviewing the milestones in attaining this understanding of the brain–immune axis integrated with numerous related studies by others. We then explain their significance in demonstrating the possibility of harnessing the immune system in a well-controlled manner for the treatment of neurodegenerative diseases. The Journal of Immunology, 2020, 204: 243–250.

Alzheimer’s disease (AD) was first identified in 1906 as a disease characterized by distinctive plaques of amyloid-β and Tau neurofibrillary tangles associated with cognitive and mental dysfunction. Since then, numerous attempts were made to reverse or, at least, to modify or attenuate this disease by targeting the accumulating proteins, with the aim of plaque elimination (1–6). Unfortunately, such attempts have largely failed (7, 8). Over the years, several other studies suggested that AD, like many other acute and chronic neurodegenerative diseases, is associated with local inflammation (9), and efforts were therefore made to reduce it by systemic generative diseases, is associated with local inflammation (9), and many other brain pathologic conditions. Over the years, several other studies suggested that AD, like many other acute and chronic neurodegenerative diseases, is associated with local inflammation (9), and efforts were therefore made to reduce it by systemic administration of steroidal or nonsteroidal anti-inflammatory drugs. Such treatments also failed to affect disease progression (10), leaving the scientific community with the question of what had been missed in the understanding of the disease (7, 11–13).

Independent basic research studies carried out by our group and others over the years strived for a deep understanding of the physiological mechanisms that maintain the healthy brain and help repair it. Such mechanisms might be lost or are insufficient under disease conditions, but could be amenable to boosting. To this end, we focused on the potential role of the immune system. When we embarked on this quest 20 years ago, even the possibility that immune cells might not be harmful to the brain and, needless to say, the suggestion that they could be beneficial was considered almost heretical.

Our journey was initiated by a simple assumption that it is inconceivable that the CNS, which is so precious and indispensable, would lack the capacity to be assisted by immune cells for its repair, whereas almost every other tissue depends on such immune support. Since then, we introduced and substantiated the essential role of the blood-borne innate and adaptive immune cells in supporting the brain during normal homeostasis and their vital role in repair following injury or facing neurodegenerative conditions (14–28). Based on these works, together with numerous additional studies by others (29–42), a new paradigm has emerged, suggesting that tightly regulated brain–immune communication is a necessary component of life-long brain maintenance and is essential for brain repair. More recently, it was found that brain–immune cross-talk is impaired in aging (43–47) and in neurodegenerative diseases (23, 48–50), and thus a fundamental mechanism of maintenance and support might be lost (23, 51) that could be amenable to restoration by rejuvenating the immune system (50–53).

These findings do not negate the original definition of the brain as an immune-privileged organ (54); they refine the understanding of the brain as an organ that, rather than functioning under complete segregation, engages in a unique and tightly regulated relationship with the immune system (55, 56). In this perspective, we describe our own scientific journey alongside with numerous related studies by others, from the original notion of systemic immune cells as destructive to the brain to their current recognition as crucial (if well controlled) (Fig. 1). We further describe the change of perspective from viewing the brain’s borders as absolute barriers between the brain and the circulation, to the current...
understanding that these borders can also serve as permissive gates for the entry of “reparative” leukocytes, as sites from which immune cells can affect the brain (37, 43, 57, 58), and as sites that can function as a lymphatic system for the brain (40, 41, 59–62). Finally, we explain the rationale underlying the shift from attempts to mitigate AD using immunosuppression to our proposal of harnessing the immune system by immunotherapy for the treatment of AD (50, 51).

Peripheral immune cell involvement in recovery from acute CNS injury

Outside the CNS, inflammation is a physiological response that is essential for tissue repair and becomes pathological if not resolved in a timely manner. As part of such peripheral “physiological” inflammation, macrophages were found to be essential players for removing dead cells and cell debris, as well as for facilitating immune resolution and tissue repair (63, 64). It is a multistep reparative process that starts with immune activation and ends with local immune resolution (19, 20, 26, 65–68). It is still debatable whether the immune resolution involves the recruitment of an additional wave of macrophages with distinct activities or whether it involves a local conversion of a single population of myeloid cells from an inflammatory to a resolving phenotype (69).

The general view, with respect to the CNS, was that it should be fully protected from immune cell entry to ensure its proper homeostasis and function. Accordingly, the failure of the CNS to recover following acute injury was often attributed to local inflammation, assuming that such inflammation might reflect, at least in part, infiltration of inflammatory cells to the site of damage, a process that should be altogether prevented or blocked (70, 71). Researchers indiscriminately viewed CNS local inflammation as an obstacle to recovery (72, 73) and to cell renewal (74–76). Therefore, it was suggested that acute treatment with steroidal anti-inflammatory drugs following spinal cord injury would promote repair (71, 77). In an apparent contrast, in animal models of acute CNS injury, including optic nerve injury (14, 67, 78), spinal cord injury (15, 16, 19, 79–82), and brain ischemia (35), it was found by our team, and subsequently by others, that blood-borne macrophages and T cells can facilitate repair. In addition, as will be discussed below, monocyte-derived macrophages were also found by several independent studies to have a role in coping with chronic brain pathologic conditions (37, 39, 78, 79, 83–92).

Peripheral immune cells in CNS homeostasis

The finding that peripheral immune cells can facilitate neural tissue protection and repair following CNS injury highlighted the possibility that the peripheral immunity might have a role in supporting CNS homeostasis and functional plasticity. To address this, initial studies focused on the hippocampus, which is known to exhibit life-long neurogenesis (95, 96), a high functional plasticity in its normal day-to-day activity, and is involved in spatial learning and memory (97, 98). It was discovered that neurogenesis, as well as spatial learning...
and memory, are impaired in young immune-compromised animals, suggesting that systemic immune cells affect healthy brain plasticity (17, 18, 29–34, 36–39, 42, 99, 100). Over the years, independent studies have identified the meninges as sites through which the immune system can affect the healthy brain. For example, T cell–derived IL-4 was found to enhance cognitive function (37). In addition, meningeal IFN-γ–producing immune cells were found to support social behavior (39). Similarly, deficiency of IFN-γ signaling from middle age onward was found to be linked to cognitive impairment (43). Other studies have suggested that the peripheral immune system supports the ability to cope with mentally stressful conditions (101–103). Along the same lines, alterations in T cell number and function have been associated with some cases of autism spectrum disorders (104–107). Taken together, these results and others have encouraged studies striving for a better understanding of the relationship between the brain and circulating immune cells.

The choroid plexus as a gateway for peripheral immune cells to the CNS. In searching for physiological sites of brain–immune communications under “sterile” acute injurious conditions, our team found that monocytes can attain access to the CNS through the leptomeninges adjacent to the lesion site and through the blood–cerebrospinal fluid barrier (BCSFB) at the choroid plexus (CP) (20, 22). Those cells that enter through the BCSFB contribute to the resolution of the inflammation within the site of pathology (20). Investigating the properties of the CP revealed that the trafficking of leukocytes through it is different from the invasion of pathological immune cells through the breached endothelium of the blood–brain barrier in diseases such as multiple sclerosis (108, 109). Thus, for example, following spinal cord injury the epithelial layer of the CP was found to be activated to express increased levels of leukocyte trafficking molecules such as CCL2, ICAM-1, and CXCL10 (22). This activity of the CP was found to be dependent on signals originating from the circulation, such as IFN-γ, and signals emerging from the brain parenchyma, via the cerebrospinal fluid, informing the CP that the brain is in distress (22). Of interest, effector memory T cells were found to populate the CP stroma and to secrete cytokines, such as IFN-γ, IL-4, and IL-10, which can modify the activity of the CP epithelium to express chemokines, cell-adhesion molecules, and growth factors (22, 48). Of note, it is not yet clear whether the cells that reside in the CP and orchestrate its activity for supporting leukocyte trafficking are the same cells that are found in the cerebrospinal fluid and the parenchyma. Over the years, the CP was found to function as a physiological gateway for immune surveillance (20, 43, 101), and a correlation was found between expression of trafficking molecules by the CP and the number of leukocytes in the cerebrospinal fluid (101). The fate of the CP following traumatic injury to the brain has not been studied. Nevertheless, under acute mental stress, the expression of leukocyte trafficking molecules by the CP was found to be affected (101). Taken together, these emerging studies have demonstrated that the meninges and the CP have multiple functions in brain homeostasis, neurogenesis, and repair (20, 37, 43, 49, 110–114).

Further studies are needed to fully describe the relationship between T cells that populate the CP, those that pass through the CP, and those that populate the meninges.

Neurodegenerative diseases and myeloid cells

Approximately 10 percent of the brain’s cells are myeloid immune cells, known as microglia (115–117). They were shown to have a distinct origin from that of macrophages and a slow rate of self-renewal (115). The microglia are maintained under tight regulation, which allows them to act as sentinels and to restore homeostasis following a mild to moderate deviation due to disturbance or damage; however, such a tight regulation restricts their ability to display a robust activity under a severe (118) or persistent pathologic condition, as in the case of chronic neurodegeneration (119). Among the factors controlling microglial activity are cell–cell interactions based on receptor/ligand pairs, such as CD200L-CD200R (120) and CX3CL1-CX3CR1 (121), and soluble factors, such as TGF-β (119, 122, 123).

The role and function of microglia in neurodegenerative diseases have not been fully elucidated. Genome-wide association studies have identified disease-associated risk factors in AD patients, many of which are immune-related genes expressed by microglia (124–127) and other immune cells (128–131). Among such risk factors is triggering receptor expressed on myeloid cells 2 (TREM2) (132–135).

Using single-cell RNA sequencing in a mouse model of AD driven by amyloid-β, a novel subset of disease-associated microglia was identified. These cells develop through a stepwise process in a TREM2-dependent fashion (124). Based on the unique RNA expression profile of these cells, it appears that they may demonstrate protective activity (124). Nevertheless, it is not clear why these activated microglia are not sufficient to mitigate the disease (118, 136). It is possible that their maturation occurs late in the disease course or that these cells are able to function only transiently and become exhausted or even destructive (137). Importantly, there is no consensus, even with respect to the role of TREM2 in microglial activity; however, several findings suggest that the role of TREM2 in microglia, positive or negative, is dependent on the stage of the disease (135, 138–143). Overall, the role of microglia in neurodegenerative conditions is still under study, and their function or dysfunction could differ among diseases and their subsets.

In addition to the resident microglia, as mentioned above, monocyte-derived macrophages are also recruited to the CNS under disease pathologic conditions. Although the function of these cells has not been fully elucidated, several studies have suggested that they play an important beneficial role in AD (23, 50, 51, 83, 85–89, 144–149). Moreover, boosting the number of monocyte-derived macrophages in different models of AD, using various immunological manipulations, was found to be beneficial in reducing the pathology and improving cognitive function (51, 146–148). These monocyte-derived macrophages were found to exhibit features associated with enhanced phagocytic activity, along with the expression of scavenger receptors and cytokines that either are not expressed by microglia or are not induced in a timely manner when needed (51, 87, 146–149). Notably, the recruitment of monocytes to the CNS was shown to be dependent on the chemokine receptor CCR2 (86). Many of the genetic AD risk factors are associated with immune activity, including factors affecting microglia and monocyte-derived macrophages. Yet, it is evident from several independent studies that in these diseases the myeloid cells within the brain are strongly affected by environmental and nutritional factors.
including ω-3 fatty acids (150), curcuminoids (151), vitamin D (152), and resveratrol (153).

It should be noted that in the past, many published studies globally referred to all myeloid cells in the brain as “microglia” with no direct distinction between myeloid cell types, and thus the conclusions might not accurately reflect the specific function of each population.

**Immunotherapy to combat AD and tauopathies.** The disappointing results in many clinical trials aimed at modifying AD by eradication of amyloid-β plaque (1–4), together with the unclear causal relationships between the levels of plaque load in the brain and cognitive loss (154–156), have argued for the presence of additional factors, which may be responsible for the cognitive impairment and thus should be targeted (11, 157–159). It is conceivable that adopting a strategy to enhance multiple mechanisms of repair would be more effective than a strategy that directly puts down a single destructive process.

In addition to the monocyte-derived macrophages, regulatory T cells are needed, as well, in restricting inflammatory conditions within the brain (23, 92). In apparent contrast, peripheral effector T cells were also found to be important players in neurodegenerative conditions (91, 160–163). Together, these studies suggest that different cell types are displaying distinct functions at the brain’s borders and within the brain parenchyma; effector T cells activate the gateway to the brain and allow trafficking through it, whereas monocytes and regulatory T cells are functioning within the site of pathology. Altogether, these results support the notion that aging and exhaustion of the immune system could contribute to the onset and escalation of neurodegenerative diseases. The challenge is how to maintain a balanced response and to orchestrate the activities of all these cell types.

Studies addressing the fate of the CP in animal models of neurodegenerative pathologies, such as AD and amyotrophic lateral sclerosis, revealed that its function as a leukocyte gateway is impaired (23, 48, 49). Restoring the function of the CP could be achieved by different strategies of boosting the peripheral immune system, including transient reduction of systemic Foxp3+ regulatory T cells (23), blocking the PD-1/PD-L1 immune checkpoint pathway (50, 51, 164), or vaccination by CNS Ags (48).

Targeting the PD-1/PD-L1 inhibitory immune checkpoint pathway in the periphery revealed that it is possible to modify disease pathology in animal models driven by amyloidosis and tauopathy (50, 51). For a long-term effect in AD and dementia, an intermittent treatment was found to be sufficient, and thus the potential for adverse immunological effects is likely to be low. Such a treatment (Fig. 2) was shown to

![FIGURE 2. Schematic representation illustrating the dynamics and the mechanism underlying the disease modification evoked by empowering the peripheral immune system by immune checkpoint blockade. The Abs (e.g., directed to PD-1 or PD-L1) that block inhibitory immune checkpoints reach circulating immune cells, lymphoid organs, and, potentially, the immune cells within the BCSFB’s stroma. The interaction between the Abs and their relevant receptors results in multiple subsequent changes in the peripheral immune system including increased levels of PD-1+ CD4+ effector memory T cells and increased availability of IFN-γ, which activates the choroid plexus epithelium to express leukocyte trafficking molecules. The enhanced ability of the CP to express these molecules supports recruitment of monocyte-derived macrophages and regulatory T cells to the brain. The monocyte-derived macrophages can directly, as well as indirectly, display multiple activities, including suppression of the inflammatory milieu of the brain via local production of IL-10, facilitating removal of amyloid-β oligomers and plaques by expressing unique scavenger receptors (e.g., MSR1). Such an immune modulation is followed by enhanced neuronal survival, rescue of synapses, and a more supportive environment for the functioning of the brain. Altogether, this multistep process leads to disease modification and cognitive improvement.](http://www.jimmunol.org/)
reduce brain inflammation, rescue neurons, and reduce brain pathology, although it is not directly targeting any specific disease hallmark. The effect was attributed, at least in part, to the enhanced homing of monocytes to the brain (50, 51), which can augment tissue repair by locally functioning as inflammation-resolving cells, and by expressing scavenger molecules (87, 89, 149). It remains to be determined whether and how resident microglia are affected by such an intervention. Temporarily reducing immunosuppressive mechanisms helps release effector T cell activity, and at the same time, maintains a sufficient number of anti-inflammatory cells in the periphery. Such a treatment approach initiates an immunological chain of events affecting the peripheral immune system as the primary target of the treatment to allow trafficking of inflammation-resolving cells to the sites of brain pathology, in which they play an essential role (23, 92, 165) (Fig. 2).

Several recent studies have suggested additional targets for immunotherapy, based on directly modulating microglia by increasing their phagocytic activity via inhibition of either CD22 (166) or CD33 (167) or by reducing the shedding of TREM2 (168).

Overall, it seems that because of the heterogeneity of AD and dementia conditions and the multiple detrimental factors (environmental and innate) contributing to the cognitive impairment and disease escalation, the targeting of a single factor (e.g., amyloid-β plaque burden, accumulation of aggregated Tau, or local neuroinflammation) is apparently not sufficient to modify such diseases. By empowering the peripheral immune system, it might be possible to overcome the difficulties of coordinately targeting multiple factors that contribute to disease escalation and cognitive impairment, which may differ between patients, and at different timepoints along the course of the disease (169). Immunotherapy, in general, could serve as a means to harness the immune system to fight this disease, independently of its primary etiology, either familial or sporadic and whether it is driven by amyloid-β, Tau, or both. Also, this therapeutic strategy might overcome the need to identify the key precipitating factor(s) leading to the initiation of the pathologic condition or additional factors whose modification is critical to arrest disease progression, or at least change its course. The fact that aging is the major risk factor of all sporadic neurodegenerative diseases supports the notion that rejuvenating the immune system could be a promising therapeutic approach.

On a personal note, the fact that 20 years ago no one would have dared to consider an option as immunotherapy for AD emphasizes how a basic scientific question can lead to a surprising mechanism-based approach (Fig. 1).

Acknowledgments
M.S. holds the Maurice and Ilse Katz Professorial Chair in Neuroimmunology.

Disclosures
M.S. is an inventor of the intellectual property that forms the basis for development of PD-L1 immunity for AD.


References


