IL-4 in the Brain: A Cytokine To Remember
Sachin P. Gadani, James C. Cronk, Geoffrey T. Norris and Jonathan Kipnis

This information is current as of July 25, 2017.

J Immunol 2012; 189:4213-4219;
doi: 10.4049/jimmunol.1202246
http://www.jimmunol.org/content/189/9/4213

References
This article cites 102 articles, 37 of which you can access for free at:
http://www.jimmunol.org/content/189/9/4213.full#ref-list-1

Subscription
Information about subscribing to The Journal of Immunology is online at:
http://jimmunol.org/subscription

Permissions
Submit copyright permission requests at:
http://www.aai.org/About/Publications/II/copyright.html

Email Alerts
Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
IL-4 in the Brain: A Cytokine To Remember

Sachin P. Gadani,*,†,1 James C. Cronk,*,†,1 Geoffrey T. Norris,*,1 and Jonathan Kipnis*,†

IL-4 has been extensively studied in the context of its role in immunity. Accumulating evidence indicates, however, that it also plays a critical role in higher functions of the normal brain, such as memory and learning.

In this review, we summarize current knowledge of the basic immunology of IL-4, describe how and where this cytokine appears to operate in normal brain function, and propose a hypothesis concerning its potential role in neurological pathologies. The Journal of Immunology, 2012, 189: 4213–4219.

The brain is frequently studied in isolation from the immune system. The principal reason for this is clear: conventional wisdom has long held that the brain is shielded from immune-cell infiltration by the blood–brain barrier (BBB). When this protective interface is breached and the immune system freely interacts with the brain, it frequently results in autoimmune attacks and other debilitating immune-related conditions. In reality, however, neuroimmune interactions appear to be crucial for everyday brain function. Mice in which adaptive immunity is absent or acutely suppressed exhibit cognitive impairment, which is expressed in their inability to perform spatial learning tasks, a defect that is reversible upon restoration of the T cell pool (1–3). One likely location for neuroimmune interactions is the subarachnoid space, a cerebrospinal fluid-filled compartment of the meninges. Healthy human cerebrospinal fluid contains ~150,000 leukocytes (~10,000 in the C57B6 mouse [our laboratory’s unpublished observations]), most of which are central memory T cells (4). A recent study from our laboratory showed that performance of a learning and memory task is followed by an increase in the numbers and activation of T cells in the meninges. Moreover, administration of anti-VLA4, which prevents normal extravasation of T cells (and monocytes) into the cerebrospinal fluid, produced a cognitive impairment similar to that seen in T cell-deficient mice (5).

T cells in the cerebrospinal fluid appear ideally positioned to communicate with the brain. In healthy individuals, however, T cells do not penetrate the brain parenchyma, and any such communication must be mediated through a soluble messenger. We recently showed that T cell-derived IL-4 is a critical participant in higher brain functions such as memory and learning (5). Mice that lack IL-4 demonstrate cognitive impairment in spatial learning tasks, and this can be reversed by transplantation of IL-4–competent bone marrow (5). In this article, we focus on the basic immunology of IL-4 as it pertains to the CNS, and in particular to the question of how and where it operates to influence cognition. We end with a review of the literature on the role of IL-4 in several neurological diseases.

IL-4 signaling

IL-4 is a cytokine that functions as a potent regulator of immunity secreted primarily by mast cells, Th2 cells, eosinophils, and basophils. Initially identified by Howard and Paul (6) as a comitogen of B cells, IL-4 was subsequently shown to be an important player in leukocyte survival under both physiological and pathological conditions (7, 8), such as Th2 cell-mediated immunity (9, 10), IgE class switching in B cells (11), and tissue repair and homeostasis through “alternative” macrophage activation (12). Although granulocytes and type 2 innate lymphoid cells (13) are capable of producing Th2 cytokines, the majority of currently available literature, including our own studies, focus on Th2 T cells.

The effect of IL-4 signaling is mediated through the IL-4R α-chain (IL-4Rα). Upon binding to its ligand, IL-4Rα dimerizes either with the common γ-chain to produce the type 1 signaling complex, located mainly on hematopoietic cells, or with the IL-13Rα1 to produce the type 2 complex, which is expressed also on nonhematopoietic cells (14, 15). The type 1 signaling complex is critical for Th2 skewing of T cells and the development of alternatively activated macrophages (AAMΦs), whereas the type 2 complex plays a role in nonhematopoietic responses to IL-4 and IL-13, for example, airway hyperreactivity and mucous production (16). The role of IL-13 in CNS function is understudied and merits further investigation.

Upon activation, the type 1 complex signals through Janus family kinases (JAK1 and JAK3), which phosphorylate and create docking sites for the transcription factor STAT6, which then dimerizes and translocates to the cell nucleus. Among its actions is the activation of the IL-13 receptor α2 (IL-13Rα2) protein.

The Journal of Immunology is published by The American Association of Immunologists, Inc. www.jimmunol.org/ cgi/doi/10.4049/jimmunol.1202246

Abbreviations used in this article: AAMΦ, alternatively activated macrophage; AD, Alzheimer’s disease; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; EAE, experimental autoimmune encephalomyelitis; GBM, glioblastoma multiforme; i.c.v., intracerebroventricularly; IL-4Rα, IL-4R α-chain; LTP, long-term potentiation; MS, multiple sclerosis; MWM, Morris water maze.

Copyright © 2012 by The American Association of Immunologists, Inc. 0022-1767/12/$16.00

*Department of Neuroscience and Graduate Program in Neuroscience, Center for Brain Immunology and Glia, University of Virginia, Charlottesville, VA 22908; †Medical Scientist Training Program, School of Medicine, University of Virginia, Charlottesville, VA 22908

1S.P.G., J.C.C., and G.T.N. contributed equally to this review.

Received for publication August 13, 2012. Accepted for publication August 27, 2012.

This work was supported by National Institute on Aging, National Institutes of Health Grant AG034113 (to J.K.).

Address correspondence and reprint requests to Dr. Jonathan Kipnis and Dr. Sachin P. Gadani, University of Virginia, 409 Lane Road, Charlottesville, VA 22908. E-mail addresses: kipnis@virginia.edu (J.K.) and sg8th@virginia.edu (S.P.G.)
other actions, STAT6 promotes transcription of GATA3 (a Th2 cell inducer) and MHCII (myeloid and B cells), and induces IgE class switching in B cells (11, 17–19). JAK1 also phosphorylates insulin receptor substrate-1 and -2, which become activated and promote survival and growth through the PI3/ AKT, PKB/mTOR, and other pathways (20).

The type 2 receptors also signal through JAK family kinases (JAK1 and TYK2), but are not expressed by T cells, and instead are used by nonhematopoietic cells such as endothelial cells and fibroblasts to respond to IL-4. As with type 1, much of the message of type 2 receptors is conveyed by STAT6, which is phosphorylated and translocates to the nucleus upon ligand binding. Type 2 receptors also serve as receptors for IL-13, a cytokine with similarities to IL-4, and that first binds with the IL-13Ra1 and then dimerizes with IL-4Rα to produce the familiar signaling cascade (Fig. 1).

**FIGURE 1.** IL-4 signaling pathways. After IL-4 binding IL-4Rα, the IL-4R is created by dimerization with the common γ-chain (γc) to create the type 1 signaling complex or with IL-13Ra1 to create the type 2 complex. Both receptors signal through STAT6, which is phosphorylated, dimerized, and traffics to the nucleus to function as a transcription factor for Th2, IgE, and AAM-associate genes. The type 1 receptor also activates IRS1 and/or IRS2, leading to increased mitogenesis and inhibition of apoptosis through multiple signaling pathways. The type 2 complex also responds to IL-13, and it can signal other STAT molecules (i.e., STAT3) through the JAK family kinase TYK2.

**IL-4 as a mediator of T cell effects on brain function**

Findings by our group and others have demonstrated a fundamental role for T cells in cognition and brain homeostasis (2, 21–24). Mice that lack T lymphocytes exhibit cognitive impairment in learning tasks on the Morris water maze (MWM). An established behavior paradigm, the MWM takes place over a week where mice are placed once daily in a large plastic pool in which a platform is submerged in opaque water. Salient visual cues are supplied in the testing room that allow the mice to gradually learn the location of the platform. Over the course of several days, a healthy mouse will commit to place over a week where mice are placed once daily in a large plastic pool in which a platform is submerged in opaque water. Salient visual cues are supplied in the testing room that allow the mice to gradually learn the location of the platform. Although T cell-deficient mice spend considerably more time searching for the platform, MWM performance can be restored almost to the level of wild-type mice by adoptive transfer of wild-type T cells or by bone marrow transplantation from wild-type to immune-deficient counterparts. In addition to their spatial learning deficits, mice that lack both T and B cells (SCID, nude, or Rag1<sup>-/-</sup> mice) exhibit reduction of adult neurogenesis (2, 24, 26), an ongoing physiological process in which new neurons are generated in specific zones of the adult brain (27). Wolf et al. (24) further identified CD4<sup>+</sup> T cells as the key immune population responsible for both adult neurogenesis and cognitive performance.

Inflammatory cytokines such IL-1β and TNF have been extensively studied in the brain, where they exert a negative effect on cognitive behavior, characterized by sickness, depression, and stress (28–30). We recently discovered that the effect of IL-4 on cognition, in contrast, is beneficial. After mice undergo training in the MWM, their meningeal T cells become activated and produce more IL-4 than untrained controls (5). Absence of the ability to produce IL-4 in response to learning has conspicuous consequences, as observed in the severe learning defects exhibited by IL-4<sup>-/-</sup> mice (5). These defects can be reversed by transplantation with wild-type bone marrow or adoptive transfer of IL-4–competent T cells, whereas both T cells and transplanted bone marrow derived from IL-4<sup>-/-</sup> mice are ineffective. Furthermore, wild-type mice transplanted with IL-4<sup>-/-</sup> bone marrow subsequently show learning impairment, reinforcing the role of IL-4 in cognition and demonstrating its dynamic nature (5).

The previously discussed findings clearly show that T cell-derived IL-4 has a profound effect on cognition, but its mechanism of action, given the stringent BBB, is unclear. Astrocytes, as described later, respond to IL-4 signaling and might serve as a mediator between the immune effector cells and the nervous responders. This possibility is supported by the fact that in wild-type mice, but not in IL-4 knockout mice, training in the MWM is followed by astrocytic production of brain-derived neurotrophic factor (BDNF) (5). This protein, which is responsible for growth and survival of neurons and for increased neuronal arborization of dendrites, has been shown to have a positive effect on learning, and its absence in IL-4 knockout mice might explain their cognitive defects (31, 32).

Another possible target for IL-4 is the meningeal myeloid compartment, where lack of IL-4 creates a proinflammatory meningeal immune response (5). Meningeal myeloid cells (CD11b<sup>+</sup>) in SCID mice produce more TNF than their wild-type counterparts (5). Adoptive transfer of wild-type T cells, but not of IL-4 knockout T cells, reduces this TNF production (5). Thus, IL-4 might be exerting its effect through an anti-inflammatory M2-skew (alternative activation) of meningeal macrophages, shown to be beneficial after CNS injury (33) and required for learning (34). Administration of M2-skewed macrophages, either intracerebroventricularly (i.e.v.) or i.v., improves MWM performance in immunocompromised animals (34). Whether these procognitive effects of T cells through astrocytes and through M2 macrophages are separate or linked processes remains to be investigated, but in either case, they provide interesting avenues for productive neuroimmune communication.
Cellular targets of IL-4 in the brain

IL-4 plays important roles in a myriad of cellular events, making it difficult to study its effects, particularly in vivo, on any one system. Although this review focuses on its neurological functions, most of what is known about IL-4 comes from studies of peripheral immune cells, such as macrophages and lymphocytes. Therefore, in discussing the cellular targets of this cytokine, we will extrapolate from those cell types where appropriate.

The earliest studies of IL-4 in macrophages showed that it acted as an anti-inflammatory agent when administered concurrently or shortly after an inflammatory stimulus, and was capable of downregulating the production of inflammatory cytokines such as TNF (35). IL-4 is not purely an anti-inflammatory agent, however, as priming of macrophages with IL-4 followed by proinflammatory stimulation can result in an enhanced inflammatory response (36). Studies in vivo showed that chronic high dosage or transgenic overproduction of IL-4 results in accumulation of AAMφs, increased IFN-γ expression, decreased proinflammatory cytokine production, histiocytosis, erythrophagocytosis, extramedullary hematopoiesis, and weight loss (37).

These data suggest that the in vivo effects of IL-4 are complex, well regulated, dependent on the local environment, and that they probably mediate different processes simultaneously in different tissues. The situation is even more complex in the context of the brain, which is clearly affected by IL-4; however, little is known about the ability of this cytokine to access the parenchyma or the nature of its effects on target cells. Microglia and astrocytes within the CNS have been studied with regard to IL-4, but the possible role of IL-4 in directly stimulating neurons and oligodendrocytes is poorly understood.

Astrocytes

As mentioned earlier, BDNF production by astrocytes might provide a mechanism whereby IL-4 influences cognition (5). BDNF may not be the only participating factor, however, as IL-4 can also elicit astrocytic expression of other CNS growth factors, such as nerve growth factor (38, 39). This function of IL-4 is not unexpected, as it can also induce other astrocytic expression of other CNS growth factors, such as nerve growth factor (38, 39). This function of IL-4 is not unexpected, as it can also induce other astrocytic expression of other CNS growth factors, such as nerve growth factor (38, 39).

The findings of the latter study thus point to a complex interplay between these two canonical Th1 and Th2 cytokines in the context of neuroprotection. Altogether, these findings show that astrocytes have a relationship to IL-4 that is complex and merits further study.

Microglia

Microglia are the brain’s equivalent of tissue-resident macrophages. Their lineage is similar to that of macrophages, although they engrave very early in development and maintain a self-renewing population throughout the lifetime of the organism (45). However, when certain conditions are met, usually involving damage, new microglia-like cells from the monocyte lineage can be engrafted into the brain of an adult animal (46).

Microglia respond comparably to macrophages in skewing paradigms (M1 and the many variants of M2) (47, 48). These include expression changes of proteins such as Ym1 and Arg1, typical of IL-4–treated macrophages. Like macrophages, microglia respond to IFN-γ priming and subsequent stimulation by upregulating NO production through induction of inducible NO synthase (49). Incubation with IL-4 before priming with IFN-γ or TNF, and subsequent stimulation with PMA, causes a dose-dependent decrease in NO production (49). Indeed, it has been shown that IL-4 exerts a neuroprotective effect via decreasing TNF and increasing IGF-1 (50). IL-4 also antagonizes IFN-γ–driven MHCII expression (51). However, IL-4 alone, after long-term exposure, also induces MHCII expression (50). CD200, a microglial regulatory protein, is expressed on neurons in an IL-4–dependent fashion, providing a possible mechanism for IL-4–mediated regulation of microglial activation. Neurons from IL-4−/− mice were found to be less effective than wild-type neurons in attenuating an inflammatory response, a result that was linked to lower CD200 expression on the IL-4−/− neurons (52). Another interesting finding was that IL-4–activated microglia can bias adult neural progenitor cells toward oligodendrogenesis (53). In addition, IL-4 was found to induce CD11c on microglia in vitro, a marker typically associated with dendritic cells (54). All in all, it seems that microglia and macrophages similarly respond to IL-4 signaling, and that absence of IL-4 heightens vulnerability to neuroinflammation. It remains unclear, however, whether IL-4 has a proinflammatory role in microglial biology, as it does in macrophages.

IL-4 in neurological pathology

IL-4 has a well-established role in the pathology of allergy and other immunological diseases, where it is secreted by T cells to induce B cell activation and IgE class switching. Less well studied, but nevertheless also important, is its influence in other diseases, including neurological ones such as Alzheimer’s disease (AD), multiple sclerosis (MS), and glioblastoma multiforme (GBM).
Inflammatory changes in the aging and AD brains

Aging in humans and rodents is accompanied by steady cognitive decline. Among the contributors to this decline is an increase in baseline inflammation. The performance of aged mice in the MWM is impaired relative to that of younger adults, in correlation with proinflammatory changes in the hippocampal and global transcriptome. Proinflammatory cytokines, such as IL-1β, IL-6, and IL-18, are increased in the aged hippocampus and are known to affect long-term potentiation (LTP), a cellular mechanism of memory whereby the strength of neuronal connections is modified.

The effects of IL-4 in aging have been reported in only a few publications, but the role of this cytokine in counteracting inflammatory changes is indisputable, and the increase in cytokines such as IL-1β and IL-6 observed in aging animals is accompanied by a decrease in hippocampal IL-4 (61). This decrease is functional, and direct i.c.v. administration of IL-4 rescues the LTP defects observed in aged mice (62). IL-4 can also counter the effects of IL-1β on LTP when coadministered i.c.v. (61). Interestingly, microglia become less sensitive to IL-4 in aged mice and tend to activate more readily, with resulting impairment of LTP (63, 64). These experiments suggest a potential role for IL-4 in countering age-related proinflammatory changes, although whether the inflammation itself derives from a lack of IL-4 signaling is not known.

The cognitive impairment seen in aged mice might be partially explained by the increase in proinflammatory cytokines and a decrease in the amount of and sensitivity to the opposing cytokine IL-4, which, in turn, disrupts LTP and impairs learning.

Many of the same inflammatory processes that operate in aging contribute to the pathology of AD, such as IL-1β–related inflammation (65, 66). IL-4 treatment can reverse certain aspects of AD pathology in animal models (Fig. 2), as shown, for example, by the finding that viral gene delivery of IL-4 to the CNS of an AD mouse model alleviates several aspects of the disease (67).

There is also a tendency toward microglial activation in AD. Microglia tend to switch from M2- to M1-like activation as AD progresses (68). The microglial regulatory molecules CD200 and CD200R are decreased in AD (69), leading to unchecked microglial activation. As described earlier, IL-4 regulates CD200/CD200R expression (52, 70), and one possible mechanism by which it exerts its effect in AD is by promoting CD200R expression on microglia, helping to quell their pathological activation (71). In addition to negating inflammatory mediators, IL-4 may confer direct benefit by inducing the IL-4–associated M2-type microglia, which have been shown in vitro to have superior amyloid-β clearance relative to M1 microglia (72, 73). In line with this, administration of amyloid-β–specific Th2 cells in the mouse model of AD improves spatial memory, decreases microglial plaque involvement, and reduces cerebral amyloid blood vessel pathology (74).

Role of IL-4 in MS

MS is a progressive demyelinating condition characterized by a relapsing and remitting course of neurological symptoms such as blurred vision, impaired balance, and paresthesias. As it progresses, MS can become increasingly debilitating and ultimately fatal. MS is often studied in rodents with experimental autoimmune encephalitis (EAE), an animal model for MS, which is induced in mice by adoptive transfer of CNS-reactive T cells or active immunization with CNS Ags. Studies of the severity of EAE in IL-4−/− mice relative to wild-type mice (75) point to a potentially protective role of IL-4 against the incidence and progression of MS.

The IL-4R is highly expressed on perivascular macrophages (76), pointing to the potential for IL-4 to regulate the myeloid compartment in animals with EAE. Microglia may help to protect the brain against autoimmunity by regulating themselves with local CNS-derived IL-4. Resting and EAE-derived microglia produce IL-4 and express Ym1 (an M2 marker), whereas infiltrating macrophages in EAE produce NO (an M1 marker) (48). Interestingly, replacement of IL-4−/− bone marrow by wild-type bone marrow does not suffice to reduce EAE severity to wild-type levels, pointing to the possibility of a brain-endogenous source of IL-4 (48). Furthermore, administration of skewed M2 cells can significantly reduce EAE severity, even when injected after disease onset in rats (77) or i.c.v. into mice (78). The molecular signaling of M2 cells was recently established further in the murine EAE model, and suggested that M2 cells can inhibit atypical EAE via SOCS3 signaling (79). These findings demonstrate the importance of myeloid skewing in MS, and suggest that IL-4 might coordinate a beneficial M2 response.

GBM and IL-4

GBM is a devastating tumor with a 5-y survival rate of ~3% (80). The role of IL-4 in cancer appears to differ from its role...
in other neurological diseases, in that it manifests somewhat contradictory protumor and antitumor effects depending on the tumor and the tissue type (81). Interestingly, the majority of GBM patient samples overexpress the IL-13Rxα2 chain (82) and the IL-4Rxα in culture (83, 84). In addition, GBM risk and outcome are altered by polymorphisms in these genes. There is a well-established inverse correlation between allergy, a disease process affected by IL-4, and GBM occurrence: individuals diagnosed with GBM are significantly less likely to report allergies (85, 86). This observation is supported by the finding that asthma-associated single nucleotide polymorphisms in the il4r, il13, and stat6 gene loci are also inversely correlated with occurrence of GBM (87, 88). Another study showed that certain polymorphisms in il4r correlate to improved GBM mortality rates (89).

These studies highlight the importance of IL-4 and IL-13 in GBM biology, but the mechanism responsible for their effect is poorly understood. Early studies demonstrated that IL-4 inhibits GBM xenograft growth in inducible IL-4ko cell lines (90) and when administered s.c. (91) or retrovirally (92). Other studies use adenoviral delivery of IL-4 under a hypoxia-inducible promoter in various GBM xenograft lines, showing marked regression of tumor growth and selective lysis of hypoxic cells after viral treatment (93, 94). IL-4 is typically thought to aid in tumor control by blocking angiogenesis (90, 95) or recruiting eosinophils (96, 97).

As tumors progress, macrophages become skewed from a proinflammatory M1 to a tumor-promoting M2 phenotype. M2 macrophages support tumor growth and survival, inducing angiogenesis (through production of vascular endothelial growth factor), creating an immunosuppressive environment, and encouraging invasiveness and metastasis (98, 99). In a nonbrain cancer model, IL-4 together with IL-10 and vascular endothelial growth factor are crucial to generation of the proinvasive M2 myeloid skew, and inhibition of IL-4Rxα in vivo blocks macrophage polarization (100). Thus, IL-4 function in GBM might be dichotomous, being used by the tumor to create AAMφs, but toxic when administered directly.

Conclusions

These studies collectively illustrate a crucial role for IL-4 in the regulation of brain immunity, with measurable downstream effects on spatial learning/memory and neurogenesis, and with implications for neurological disorders. From the data reviewed in this article, it is tempting to assume that an “alternative” IL-4-driven activation of the immune system supports brain function, whereas molecules with classic proinflammatory “signals” hinder it. This view may, however, be an oversimplification of complex neuroimmune interactions taking place in boundaries of the brain and in the brain parenchyma. Although proinflammatory cytokines have been implicated in the detrimental effects of sickness behavior, aging, and autoimmunity, it is likely that a proper balance in peripheral and brain immunity is required for optimal brain performance. In fact, certain cytokines associated with classical inflammation are required for many aspects of vital CNS function such as synaptic scaling through glial TNF (101) and the role of IL-6 in ensuring functional LTP in the hippocampus (102).

In times of stress and disease, the delicate balance in brain immunity is altered, with proinflammatory molecules produced to a high degree in response to a potential threat (28). Production of IL-4 by meningeal T cells and other cell types could therefore be viewed in terms of an evolutionary adaptation to restore balanced CNS function and cognition. New molecular and genetic tools that target IL-4, IL-13, and their receptors in specific cell types will advance the field and further our understanding on the precise roles of T cell-derived and non-T cell-derived IL-4 in the regulation of brain function.

Although replacing or even directly altering CNS cells represents a substantial technical challenge, in part because of the BBB, the immune system is more easily targeted by drugs and can even be replaced by means of bone marrow transplantation. Therefore, a better understanding of the effects of the immune system on CNS function will open new therapeutic avenues for diseases that have traditionally been approached as purely neurological, but that have important and treatable immune components (103).

Acknowledgments

We thank Shirley Smith and Nicola Watson for editing the manuscript. We thank the members of the Kipnis laboratory for valuable comments during multiple discussions of this work.

Disclosures

The authors have no financial conflicts of interest.

References


in mice lacking the interleukin 13 receptor alpha1 chain.  


Lee, G. R., P. E. Fields, T. J. Griffin, and R. A. Flavell. 2003. Regulation of the  
Th2 cytokine locus by a locus control region.  

Luzina, I. G., A. D. Keghan, N. M. Heller, G. A. Root, T. Shea-Donohue, and  
of “alternatives.”  

leads to cognitive dysfunction: implications for therapeutic vaccination for  
schizophrenia and other psychiatric conditions.  

function: a conceptual model.  

drives microglia to the M2 phenotype: implications for brain injury and  
anti-inflammatory conditions: Effects of oligomeric and fibrillar amyloid-beta.  

Ponomarev, E. D., K. Mareas, Y. Tan, and B. N. Dimire. 2007. CNS-derived  
interleukin-4 is essential for the regulation of central neuroinflammation  
and induces a state of alternative activation in microglial cells.  

phenotype by an oligomeric amyloid-beta peptide: a role for interleukin 4?  

Butovsky, O., A. E. Talpalar, K. Ben-Yaakov, and M. Schwartz. 2005. Activation of  
microglia by aggregated beta-amyloid or lipopolysaccharide impairs MHC-II  
expression and renders them cytotoxic whereas IFN-gamma and IL-4 render them  
proinflammatory.  

Alliot, F., I. Godin, and B. Pessac. 1999. Microglia derive from progenitors,  
originating from the yolk sac, and which proliferate in the brain.  

Milderer, A., H. Schmidt, M. Nitsche, D. Merkler, U. K. Hanisch, M. Mack,  
M. Heikenwalder, W. Brückl, J. Priller, and M. Prinz. 2007. Microglia in the adult  
brain arise from Ly-6Ch/C-CR3+ monocytes only under defined host conditions.  

Characterization of the microglial phenotype under pro- and anti-inflammatory  
conditions: Effects of oligomeric and fibrillar amyloid-beta.  

of “alternatives.”  

leads to cognitive dysfunction: implications for therapeutic vaccination for  
schizophrenia and other psychiatric conditions.  

function: a conceptual model.  

drives microglia to the M2 phenotype: implications for brain injury and  
anti-inflammatory conditions: Effects of oligomeric and fibrillar amyloid-beta.  

Ponomarev, E. D., K. Mareas, Y. Tan, and B. N. Dimire. 2007. CNS-derived  
interleukin-4 is essential for the regulation of central neuroinflammation  
and induces a state of alternative activation in microglial cells.  

phenotype by an oligomeric amyloid-beta peptide: a role for interleukin 4?  

Butovsky, O., A. E. Talpalar, K. Ben-Yaakov, and M. Schwartz. 2005. Activation of  
microglia by aggregated beta-amyloid or lipopolysaccharide impairs MHC-II  
expression and renders them cytotoxic whereas IFN-gamma and IL-4 render them  
proinflammatory.  

Alliot, F., I. Godin, and B. Pessac. 1999. Microglia derive from progenitors,  
originating from the yolk sac, and which proliferate in the brain.  

Milderer, A., H. Schmidt, M. Nitsche, D. Merkler, U. K. Hanisch, M. Mack,  
M. Heikenwalder, W. Brückl, J. Priller, and M. Prinz. 2007. Microglia in the adult  
brain arise from Ly-6Ch/C-CR3+ monocytes only under defined host conditions.  

Characterization of the microglial phenotype under pro- and anti-inflammatory  
conditions: Effects of oligomeric and fibrillar amyloid-beta.  

of “alternatives.”  

leads to cognitive dysfunction: implications for therapeutic vaccination for  
schizophrenia and other psychiatric conditions.  

function: a conceptual model.  

drives microglia to the M2 phenotype: implications for brain injury and  
anti-inflammatory conditions: Effects of oligomeric and fibrillar amyloid-beta.  

Ponomarev, E. D., K. Mareas, Y. Tan, and B. N. Dimire. 2007. CNS-derived  
interleukin-4 is essential for the regulation of central neuroinflammation  
and induces a state of alternative activation in microglial cells.  

phenotype by an oligomeric amyloid-beta peptide: a role for interleukin 4?  

Butovsky, O., A. E. Talpalar, K. Ben-Yaakov, and M. Schwartz. 2005. Activation of  
microglia by aggregated beta-amyloid or lipopolysaccharide impairs MHC-II  
expression and renders them cytotoxic whereas IFN-gamma and IL-4 render them  
proinflammatory.  

Alliot, F., I. Godin, and B. Pessac. 1999. Microglia derive from progenitors,  
originating from the yolk sac, and which proliferate in the brain.  
cancer cells express interleukin-4 (IL-4) receptors which are targets for the toxic
receptor for interleukin 13, a brain tumor-associated cancer/testis antigen.
Cancer Res. 65: 6459–6465.
89. Ruan, Z., Y. Zhao, L. Yan, H. Chen, W. Fan, J. Chen, Q. Wu, J. Qian, T. Zhang,
K. Zhou, et al. 2011. Single nucleotide polymorphisms in IL-4RA, IL-13 and
STAT6 genes occurs in brain glioma. Front Biosci (Elite Ed) S:33–45.
87. Schwartzbaum, J., A. Aihlimb, B. Malmer, S. Lönn, A. J. Brooks, H. Dou,
with asthma are inversely related to glioblastoma multiforme. Cancer Res. 65:
6459–6465.
88. Ruan, Z., Y. Zhao, L. Yan, H. Chen, W. Fan, J. Chen, Q. Wu, J. Qian, T. Zhang,
K. Zhou, et al. 2011. Single nucleotide polymorphisms in IL-4RA, IL-13 and
STAT6 genes occurs in brain glioma. Front Biosci (Elite Ed) S:33–45.
87. Schwartzbaum, J., A. Aihlimb, B. Malmer, S. Lönn, A. J. Brooks, H. Dou,
with asthma are inversely related to glioblastoma multiforme. Cancer Res. 65:
6459–6465.