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Brain homeostasis is maintained by "danger" signals stimulating a supportive immune response within the brain's borders

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ABSTRACT

An organism's behavior is determined by the way it senses and perceives the surrounding environment, and by its responses to these stimuli. The major factors known to affect the behavioral response to an event are genetic background, environmental factors, and past experiences, and their imprinting on the relevant brain circuits. Recently, circulating immune cells were introduced as novel players into this system. It was proposed that the brain and circulating immune cells engage in a continuous dialogue that takes place within the brain's territory, though outside the parenchyma (occurring within the brain's borders – the choroid plexi, the brain meninges and the cerebrospinal fluid (CSF)). The cytokines secreted by activated leukocytes residing at the borders were shown to affect neurotrophic factors production within the parenchyma. Here, we suggest that such a dialogue is stimulated at the brain's borders, upon need, by a "danger" signal that originates in the parenchyma in response to any destabilizing event, and discuss the potential role of reactive oxygen species (ROS) in transmitting this signal. Accordingly, a failure to restore balance is likely to lead to aberrant responses to subsequent events. This view thus supports the contention that circulating immune cells are required to maintain the brain's balanced activity and suggests a novel mechanism whereby the surveying immune cells are sensing the brain's status and needs.

1. Introduction

1.1. Factors shaping subjective behavior

When challenged by an external stimulus, an individual's behavior is directed towards evaluating the destabilizing potential of the stimulus. The interface between the incoming information and the evaluation process is formed within limbic brain structures, which include the hippocampus, amygdala and prefrontal cortex. These structures integrate the physiological, emotional, and memory components of the individual's reaction to the stimulus (Sullivan et al., 2006). The two major factors known to determine the perception of an event and the consequential response are genetic background (Binder et al., 2010; Jovanovic and Ressler, 2010) and past experiences (McCauley et al., 1997; Sullivan et al., 2006), and their imprinting on the limbic and stress-response systems.

Experiences that are most likely to leave their mark on the wiring patterns of the limbic synaptic systems are those encountered during infancy and early childhood, times which are considered critical for the fine tuning of neuronal wiring (Sullivan et al., 2006). For example, filial imprinting, the process by which an emotional bond to the mother or caregiver is formed, causes changes in synaptic connectivity in prefrontal forebrain regions (Sullivan et al., 2006). While experience-dependent fine-tuning provides an optimal adaptation of the brain to a given environment, when synaptic reorganization is driven by an adverse environment, it could result in "defective" synaptic wiring that will cause aberrant behavior throughout life (Andersen and Teicher, 2004). In addition, traumatic experiences at any stage were shown to cause an over sensitization of the central stress response system (McGuire et al., 2010; Coplan et al., 1996; Bhatnagar and Dallman, 1998; Ulrich-Lai et al., 2007; Heim et al., 2008; Zoladz et al., 2008). Normally, the adaptive stress response is coordinated by secretion of two neuropeptides: corticotropin-releasing hormone (CRH) and vasopressin (AVP), which are secreted by the hypothalamus and activate the HPA axis, resulting in secretion of corticosteroid hormones. The spread of corticosteroids through the circulation allows the coordination of brain and somatic functions that are geared towards coping with stress, recovery and adaptation (reviewed in: (de Kloet et al., 2005)). Hypersensitivity of the HPA axis due to traumatic childhood experience increases the risk of developing depression later in life in response to stress (Heim et al., 2008). Similarly, patients with post traumatic stress disorder (PTSD) show elevated CRH levels in their cerebro-spinal fluids (CSF) (Bremner

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et al., 1997), and enhanced secretion of cortisol following a traumatic event (Elzinga et al., 2003).

Regardless of past mental experiences or episodes, evidence suggests that immune related dysfunction, either congenital or as a result of a postnatal event, could, by itself, lead to behavioral, mental or cognitive malfunctions at adulthood. For example, strong activation of an immune response during pregnancy was shown to cause a persistent immune abnormality in the offspring (Mandal et al., 2010; Yamaguchi et al., 1983; Fujii and Yamaguchi, 1992; Cardon et al., 2010). These offspring show increased susceptibility to various mental disorders, such as schizophrenia, and autism (Ciaranello and Ciaranello, 1995; Shi et al., 2003; Brown, 2006). Similarly, infection during early childhood is correlated with subsequent development of Tourette syndrome (Church et al., 2003). A recent study by our group demonstrated that congenital immune deficiency in mice causes abnormal sensorimotor gating (Cardon et al., 2010), an activity that is impaired in schizophrenia (Swerdlow et al., 2006), as well as in other neuropsychiatric disorders (Swerdlow et al., 1993, 1995; Castellanos et al., 1996). Another example connecting immune profile to mental health is the case of post traumatic stress disorder (PTSD), in which a specific gene expression pattern in peripheral blood mononuclear cells of patients hospitalized immediately following the experience of a stressful event predicted emergence of PTSD (Segman et al., 2005). One possible explanation for these findings is that such immune abnormalities, similar to the defective neuroendocrine stress response, impair the individual's ability to cope with stressful life events, thus increasing the susceptibility to develop behavioral abnormalities.

Several studies done in our laboratory over the last few years provided the basis for the hypothesis that links adaptation to stress with the presence/activity of circulating immune cells by showing that the presence of a functional adaptive immune system at the time of exposure to mental stress reduces susceptibility to post-traumatic behavioral abnormalities (Cohen et al., 2006; Lewitus et al., 2008, 2009). In this perspective article, we suggest that protective immune-derived factors are produced by the circulating immune cells within the brain's borders in response to an alarm signal that is emitted by the stimulated brain (Fig. 2).

1.2. Interaction of systemic immune cells with the brain

The first line of immune defense within the CNS is mediated by microglia, which are the resident macrophages of the CNS parenchyma (McKercher et al., 1996; Ransohoff and Cardona, 2010). Although previously referred to as "resting" cells, it is now becoming clear that microglia continuously sample their environment to monitor changes in CNS homeostasis (Nimmerjahn et al., 2005), and rapidly respond to threats (Davalos et al., 2005). It has been suggested that microglia are able to polarize their activation state to achieve the appropriate responses to varying challenges (Ransohoff and Perry, 2009), in a manner similar to peripheral macrophages (Geissmann et al., 2010; Martinez et al., 2009).

In addition to the monitoring performed by resident microglia, systemic immune cells are also engage in a constant immune surveillance of the CNS that takes place primarily within the CSF. Such immune surveillance is carried out primarily by memory T cells, which were shown to migrate from the blood to the CSF through the choroid plexus and meninges, and comprise 80% of the cells in the CSF of healthy individuals (Ransohoff et al., 2003). Furthermore, the continuous circulation of T cells between the periphery and the CNS was demonstrated. T cells re-enter the bloodstream from the CSF and are replaced by new lymphocytes approximately every 12 h (Kivisakk et al., 2003; Ransohoff et al., 2003; Engelhardt and Ransohoff, 2005; Reboldi et al., 2009). The initial encounter of naïve T cells with neuroantigens occurs mainly in the peripheral lymphatic organs. Despite the lack of classical lymphatic vessels in the CNS, there are indications for drainage of CNS antigens to the CSF circulatory pathway, finally reaching the deep cervical lymph nodes, the nasal lymphatics and the spleen, via the circulation (Ransohoff et al., 2003; Engelhardt and Ransohoff, 2005). While circulating within the CSF, the T cells can be reactivated by encountering their cognate antigen presented by APCs that populate the choroid plexus, the CNS meninges, and the perivascular and sub-arachnoid spaces (McMenamin et al., 2003; Ransohoff et al., 2003; Kawakami et al., 2004).

The entrance of T cells through the choroid plexus into the territory of the CNS was primarily investigated to explain the initiation of neuroinflammation. It was demonstrated that the first wave of encephalitogenic T cells enter the CNS through the choroid plexus (Reboldi et al., 2009). Their subsequent reactivation in the CSF induces expression of adhesion molecules on the cerebral blood vessel endothelium, enabling the penetration of a second wave of T cells to the parenchyma (Bartholomaus et al., 2009; Reboldi et al., 2009). Several molecules that are expressed on the choroid plexus epithelium were found to mediate the penetration of T cells, including CCL20, which binds to CCR6 on the T cells (Reboldi et al., 2009), CD73 (Mills et al., 2008), and P-selectin (Kivisakk et al., 2003). In the following section we will discuss recent lines of evidence suggesting a fundamental role for these surveying T cells in supporting normal brain function and plasticity.

1.3. Systemic immune cells support brain function and plasticity

The need for systemic immune cells to support brain function and plasticity was first demonstrated using immune deficient mice, and mice lacking specific immune-cell populations. It was found that adult neurogenesis, neurotrophic factor production, and hippocampus-dependent functions such as spatial memory and sensorimotor gating are all dependent on immune cell availability (Kipnis et al., 2004; Ziv et al., 2006; Brynskikh et al., 2008; Ron-Harel et al., 2008; Wolf et al., 2009a,b; Cardon et al., 2010). Apparently, the immune-brain dialogue needed for normal brain function under physiological conditions occurs within the brain's territory and is mediated by the CNS-surveying T cells: A recently published study demonstrated that hippocampus-dependent cognitive ability is specifically supported by the T cells that reside within the brain meninges (Derecki et al., 2010). The "long-distance" communication between the relevant brain structures (i.e. hippocampus) and the T cells might be mediated by cytokines that are secreted in the meninges and arrive at the parenchyma through the CSF. Specifically, it was shown that IL-4, which is secreted by meningeal resident T cells, supports spatial memory performance by induction of BDNF production in the hippocampus (Derecki et al., 2010). The need for immune-cell activity to ensure normal brain function is ongoing: Sudden T cell depletion in young healthy adult mice causes cognitive impairment, whereas immune reconstitution restores spatial memory abilities in immune deficient mice (Brynskikh et al., 2008; Ron-Harel et al., 2008). The specific cells that support normal cognitive performance and neurogenesis are CNS-specific autoreactive $CD4^+$ T cells. This observation was based on the comparison made between: Tova-transgenic mice, in which the majority of the T cell population is specific to the non-self antigen (ovalbumin), and Tmbp-transgenic mice, in which the majority of the T cell population is specific to the CNS antigen myelin basic protein (MBP). While Tmbp-transgenic mice showed normal cognitive ability and increased hippocampal neurogenesis, the Tova-transgenic mice resembled immune deficient mice in their impaired cognitive ability, and their reduced hippocampal neurogenesis (Ziv et al., 2006).

Increased T cell numbers are found in the borders of the CNS following increased brain activity (i.e. cognitive testing (Derecki et al., 2010) and acute mental stress (Lewitus et al., 2008)). These

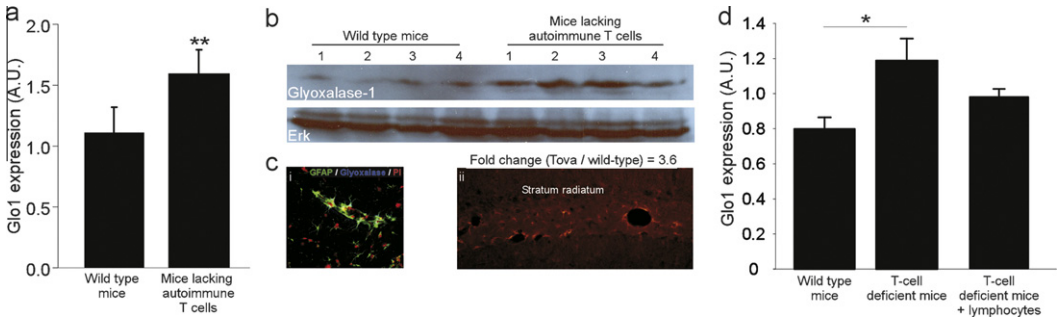

Fig. 1. Skewed T cell repertoire results in increased expression of the carbonyl detoxification enzyme Glyoxalase-1 in the hippocampus and choroid plexus. Glyoxalase-1 expression in the hippocampus of wild type ($n = 6$) mice and mice lacking autoimmune T cells (Tova-transgenic mice (Ziv et al., 2006); $n = 9$) was measured by real-time PCR (a; $t7.2 = 4.8$; $P = 0.001$) and by Western blot (b; $t3.97 = 5.6$; $P = 0.005$). (c) Immunohistochemical staining for Glyoxalase-1 demonstrated its expression by astrocytes (GFAP + cells) (i), in the statum radiatum of the hippocampus (ii). (d) T-cell deficient (nude) mice on a Balb/c background were transplanted with T cells from wild type donors of the same genetic background, and tested for *Glo1* expression in the choroid plexi by real-time PCR, 4 weeks following transplantation. *Glo1* expression was higher in nude mice ($n = 5$) compared to wild type controls ($n = 6$), and was reduced following immune reconstitution ($n = 5$) (ANOVA: $F2,12 = 5.31$, $P = 0.02$; $^*P < 0.05$; Fisher LSD post hoc analysis). Error bars represent SEM.

findings, taken together with the contribution of systemic immune cells to successful coping with mental stress (Cohen et al., 2006), raise the question as to whether local cytokine secretion by T cells within the brain's territory (in the choroid plexus/meninges/CSF) can restore balance following any mental activity, thereby ensuring an adequate behavioral response to subsequent stimuli (Fig. 2).

2. Protective autoimmunity: Circulating immune cells reduce neuroinflammation

Proinflammatory cytokines are abundantly expressed in the healthy brain (Vitkovic et al., 2000; O'Connor et al., 2009) and are involved in the regulation of many physiological functions such as pain sensitivity, memory consolidation, and neural plasticity (Avital et al., 2003; Wolf et al., 2003, 2006; Shavit et al., 2005; Goshen et al., 2007). Elevation in brain cytokine levels is considered part of the adaptive response to external stimuli; for example, exposure to acute psychological stressors, by induction of catecholamines (adrenalin, noradrenalin, and dopamine), induces an increase in brain proinflammatory cytokines (including TNFα, IL-1β and IL-6) (Bierhaus et al., 2003; Johnson et al., 2005), which modulate the neuroendocrine and behavioral responses to the stressor (Berkenbosch et al., 1987; Bernton et al., 1987; Turnbull and Rivier, 1999; Butterweck et al., 2003; Goshen et al., 2003; Harden et al., 2008; Abraham and Johnson, 2009; Goshen and Yirmiya, 2009).

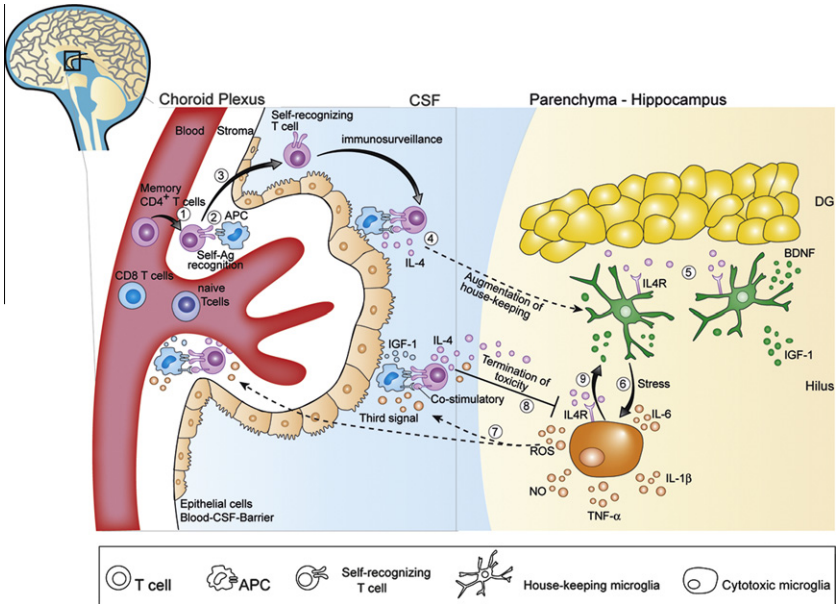

Fig. 2. A model describing the molecular mechanism of immune-mediated resolution of mental stress. This scheme summarizes our view of how the parenchyma signals for help to the circulating immune cells that reside within the brain's territory but outside the parenchyma. Frames (1–5) describe T-cell mediated support of brain housekeeping, and frames (6–9) describe their involvement in restoration of homeostasis following exposure to stress. Memory T cells enter the cerebrospinal fluid (CSF) by transmigration from blood vessels into the stroma of the choroid plexus (CP) (1). $CD4^+$ memory T cells are primed in the CP by antigen-presenting cells (APCs) presenting CNS-self-antigen (Ag) (2). Upon recognition of self-Ag, T lymphocytes cross the epithelial blood-CSF-barriers into the CSF (3). Reactivation within the CP or the CSF by MHC-II-expressing APCs results in the secretion of T cell-derived cytokines, and specifically IL-4, into the CSF (4). IL-4 reaches the parenchyma through the CSF circulation, and induces secretion of neuroprotective substances (i.e. BDNF and IGF-1) by local microglia (5). Exposure to acute psychological stress induces a proinflammatory phenotype in resident microglia, characterized by secretion of reactive oxygen species (ROS), NO, and increased levels of proinflammatory cytokines (i.e. IL-1β, TNFα and IL-6) (6). Our model suggests that ROS exit the parenchyma to the CSF and serve as the "third signal", in addition to the T-cell receptor (TCR) and co-stimulatory signals (CD28/CD80,86), which facilitate T cell activation despite low antigen presentation (7). This stimulation occurs either by acting directly on T cells or by priming the APCs. T cells activated in response to increased toxicity are expected to secrete increased levels of IL-4, which then penetrates the parenchyma, and binds to IL4R on the cytotoxic microglia (8). Exposure of cytotoxic microglia to IL-4 causes downregulation of proinflammatory factor secretion, and induces expression of neuroprotective factors (BDNF, IGF-1), which support restoration of homeostasis (9). Modified from (Schwartz and Shechter, 2010).

The immediate source of neuroinflammatory cytokines may be activated microglia: administration of a microglial inhibitor blocks stress-dependent elevation of IL-1β secretion in the hypothalamus (Blandino et al., 2006). Excessive levels of proinflammatory cytokines (in response to chronic stress exposure, or loss of regulatory mechanisms that terminate the adaptive stress response) initiate an inflammatory reaction (Olivenza et al., 2000; Madrigal et al., 2001, 2002) that could lead to long-lasting behavioral abnormalities and neurodegeneration (Gilhotr et al., 2010; Koo et al., 2010; Allan and Rothwell, 2003; Dhir et al., 2006; Gilhotra and Dhingra, 2009; Goshen and Yirmiya, 2009; Koo and Duman, 2009; Lindqvist et al., 2009). Similar etiology of the local brain inflammatory response is also seen in other extreme conditions such as acute CNS injury and neurodegeneration (Di Filippo et al., 2010; Glass et al., 2010). In both cases, brain microglia are activated in response to the abnormal elevation in endogenous agents (i.e. amyloid-β) and secrete proinflammatory substances such as TNFα, IL-1α and β, IL-6, iNOS, COX-2, and NFκb (Laskin and Pendino, 1995). Such activated microglia, although effective for the removal of the pathological factor(s), constitute a threat to the delicate neuronal tissue if they become chronically activated.

Studies performed by our group and others over the last decade distinguished this detrimental local neuroinflammatory response from the benefit exerted by systemic immune-cell activation (Moalem et al., 1999; Hammarberg et al., 2000; Hauben et al., 2000; Frenkel et al., 2003; Benner et al., 2004; Simard et al., 2006; Boissonneault et al., 2009; Skihar et al., 2009). We showed that recruitment of systemic immune cells promotes the termination of the local neurotoxic inflammatory response (Shechter et al., 2009). This protective response, controlled by the systemic-immune system, is mediated by circulating T cells specific to CNS antigens (Moalem et al., 1999; Hauben et al., 2000; Shechter et al., 2009) that contribute to modifying microglial activity, and to boosting infiltration of blood–borne monocytes upon need (Shechter et al., 2009). The infiltrating macrophages, together with the microglia that they regulate, remove dead cells and cell debris, buffer toxic compounds (such as glutamate and reactive oxygen species), and produce growth factors needed for cell survival and renewal, while downregulating inflammation-associated compounds such as IL-1β, TNFα, iNOS and COX-2 (Hauben et al., 2000; Butovsky et al., 2007; Rolls et al., 2008; Shechter et al., 2009). The phenotype of microglia activated by T cell-derived cytokines is distinct from that of microglia activated by pathogen-related compounds (i.e. LPS) or endogenous cytotoxic agents (i.e. amyloid-β). Microglia or blood-borne macrophages exposed to T-cell derived cytokines (i.e. IL-4, IFNγ) acquire neuroprotective features that are manifested by reduced secretion of proinflammatory cytokines (i.e. TNFα, IL-6) and increased secretion of insulin like growth factor-1 (IGF-1) (Butovsky et al., 2005; Butovsky et al., 2006a,b; Shaked et al., 2005; Beers et al., 2008; Chiu et al., 2008; Shimizu et al., 2008; Koronyo-Hamaoui et al., 2009). IGF-1 was shown to enhance neuroprotection under various conditions of brain pathology and neurodegeneration (Zheng et al., 2000). Notably, astrocytes also acquire a neuroprotective phenotype following their co culture with T cells (Garg et al., 2008, 2009).

The entire concept attributing a beneficial role to autoreactive T cells in CNS protection, repair and maintenance that was collectively named by our group as 'Protective autoimmunity' (Moalem et al., 1999), does not imply that all T cells that recognize CNS antigens are beneficial and under all circumstances. If the autoreactive response escapes regulation it could lead an autoimmune disease. Such a regulation that enables a beneficial autoimmune disease controls the specificity and affinity of the participating cells, and the timing, location and duration of their response.

As mentioned earlier, a specific role was attributed to the T cell cytokine, IL-4, in supporting normal brain function (Derecki et al., 2010). Lack of IL-4 negatively affects cognition, whereas increased brain activity (i.e. that induced by cognitive testing), results in elevation in T cell numbers, and in IL-4 expression within the meninges (Derecki et al., 2010). Interestingly, in vitro studies identified IL-4 as a critical cytokine for counteracting neuroinflammation (Butovsky et al., 2005). Of special interest are the following observations: (1) Microglia activated by IL-4 remain committed to their protective phenotype even when exposed to a threatening environment in the form of LPS or aggregated β-amyloid, and can counteract the threat. (2) Exposure of microglia pre-activated to a cytotoxic phenotype to IL-4 induces a phenotype switch towards neuroprotection (Butovsky et al., 2005; Schwartz et al., 2006).

Thus, brain cytokine levels must be under constant regulation to enable normal brain function and a rapid response upon need, with an efficient and fast return to homeostasis (Fig. 2). Here, we suggest that such regulation of the brain milieu is mediated by circulating immune cells at the borders of the CNS, according to the following scenario: Any destabilization in brain homeostasis that cannot be locally contained by the microglia and/or astrocytes, will increase recruitment of systemic T lymphocytes to the brain territory (Lewitus et al., 2008), and their local secretion of cytokines, such as IL-4 into the CSF (Derecki et al., 2010). Exposure to IL-4 is expected to downregulate secretion of proinflammatory cytokines and upregulate secretion of neurotrophic factors (i.e. IGF-1, BDNF) by activated microglia (Fig. 2). Moreover, the fact that a primary exposure to IL-4 improves future resilience to toxic conditions (Butovsky et al., 2005) suggests an immunological mechanism whereby previous exposures to mildly stressful conditions improve stress resilience (Lewitus and Schwartz, 2009). This suggested pathway assumes the ability of the stressed parenchyma to signal to the T-cells residing at its borders (Fig. 2). How might this occur?

2.1. Redox signaling – the brain parenchyma's call for help

A successful T cell mediated response requires the combination of T cell receptor (TCR) activation by specific cognate antigen, together with activation of costimulatory molecules (the binding of CD28 on the T lymphocyte to CD80/86 on the antigen presenting cell) (Jenkins and Johnson, 1993), and a third signal that is mediated by proinflammatory cytokines, and is essential for inducing, enhancing and prolonging the antigen-specific CD4 T cell response (Curtsinger et al., 1999). The third signal often depends on the production of reactive oxygen species (ROS) at the site of inflammation (Tse et al., 2007). Such ROS stimulate the generation of proinflammatory cytokines by APCs, through activation of redox-sensitive signal transduction pathways such as MAPK, AP-1, and NFkb (Lander et al., 1995; Suzuki et al., 1997; Rao, 2001; Matsuzawa et al., 2005). Accordingly, interfering with the redox balance by down regulating ROS production by APCs leads to reduced T cell effector function, as manifested by reduced proliferation and cytokine secretion (Tezel et al., 2007; Tse et al., 2007; Sklavos et al., 2008). In response to immunization, the ROS-dependent signal is induced by the adjuvant properties of the CFA, LPS or other microbial products (Pape et al., 1997; Curtsinger et al., 1999). ROS might also have a direct effect on effector T cells; superoxide and/or physiologically relevant concentrations of hydrogen peroxide were shown to augment the production of interleukin-2 by T cells stimulated with antigen or mitogen in various experimental systems (Roth and Droge, 1987; Los et al., 1995). Importantly, exposure of T lymphocytes to physiological concentrations of environmental ROS or to other inducers of moderate oxidative stress does not bypass the requirement for signaling cascades initiated by specific cell membrane receptors (TCR, CD3, CD28), though ROS exposure can amplify signaling cascades after relatively weak receptor stimulation (Hehner et al., 2000). Thus, ROS from the inflammatory

environment appear to decrease the triggering thresholds of the antigen receptor-dependent signal cascades. Such redox-mediated augmentation of the immune response was suggested as a mechanism that allows the initiation of an effective immune response even before large amounts of antigen have accumulated (Droge, 2002).

Whereas in the rest of the body, antigen presenting cells and T cells migrate to the site of infection where antigen concentrations are highest, in the case of the CNS, immune cells that are located at the "borders of the CNS" must respond to distant events that occur within the parenchyma. Thus, a mechanism that reduces the threshold of antigen that is able to initiate a response is crucial. We suggest that following exposure to mental stress, the activation of leukocytes residing in the brain borders is facilitated, from afar, by redox signals emanating from the brain parenchyma due to the stress-induced neuroinflammatory response (Fig. 2). Accordingly, in other models of brain pathologies that involve neuroinflammation, it was demonstrated that parenchymal oxidative stress is reflected in the CSF (Montine et al., 1998; Greco et al., 1999). Thus, behavioral maladaptation and increased susceptibility to mental illness that result from a deficiency in circulating immune cells during exposure to psychological stress, might be due to the skewed cytokine profile at the CNS borders (Derecki et al., 2010), and to the lack of T-cell derived cytokines such as IL-4 able to counteract neuroinflammation and restore brain homeostasis (Fig. 2).

The potential role of circulating immune cells in resetting brain homeostasis is most probably not restricted to extreme conditions. Since immune competence is essential for normal brain function at all times (Brynskikh et al., 2008; Ron-Harel et al., 2008), it is plausible that the CNS and circulating immune cells are engaged in an ongoing dialogue whereby the immune cells residing at the borders of the CNS respond to any changes in parenchymal homeostasis that occur as part of normal brain function and that are not contained locally (Nimmerjahn et al., 2005; Hanisch and Kettenmann, 2007). If this is indeed the case, then we would expect to find evidence of accumulated toxicity in the brains of immune-deficient mice as a result of life-long events that were not properly terminated to restore homeostasis. In the following section, we discuss preliminary findings that support this notion.

2.2. Elevation of detoxification mechanisms in the brains of mice lacking CNS-specific autoreactive T cells

Our model suggests that chronic immune malfunction will result in accumulation of toxic factors and the ensuing recruitment of local detoxification mechanisms to counteract them. In a study performed in our laboratory to identify activation of such mechanisms, we performed screening by gene array (Affymetrix MOE430A), comparing hippocampal RNA extract taken from normal Balb/c mice, and mice lacking T cells recognizing brain antigens on a Balb/c background. The screen identified an elevation in expression of *Glo1* (fold change = 2.6, $P < 0.001$), the gene encoding Glyoxalase-1, in the brains of the mice bearing a skewed T cell repertoire. The difference in *Glo1* expression was further verified both on the mRNA level by real-time PCR (Fig. 1a) and on the protein level, by Western blot analysis (Fig. 1b).

Glyoxalase-1 is part of the Glyoxalase detoxification mechanism, which degrades reactive α-oxoaldehydes that are produced as part of normal metabolism (Vander Jagt and Hunsaker, 2003) and as a result of oxidative processes (e.g. lipid peroxidation and oxidative degradation of glucose), and which are augmented under increased oxidative stress (Thornalley et al., 1999; Ramasamy et al., 2005). Normally, Glyoxalase-1 levels in the CNS parenchyma are enhanced with increased age, as a compensatory mechanism against increased free radical and carbonyl levels (Sharma-Luthra and Kale, 1994; Kuhla et al., 2006).

Although the brain parenchyma has the enzymatic capacity to detoxify reactive compounds, for example, through glutathione (GSH) (Monks et al., 1999), most of the activity of the detoxifying machineries occurs at the blood–brain interfaces. These interfaces include the cerebral capillaries forming the BBB, and the choroid plexi, which express high levels of detoxifying and metabolizing enzymes (Emerich et al., 2005). Comparing Glyoxalase-1 expression in the choroid plexi of T-cell deficient compared to wild-type mice demonstrated an elevation similar to that found in the hippocampus. In support of the ongoing requirement for T cells, reconstitution of the T cell pool reduced Glyoxalase-1 levels to normal (Fig. 1d). These results provide indirect evidence that conditions characterized by immune deficiency result in accumulation of toxicity in the CNS parenchyma.

In summary, our model suggests that the brain parenchyma and the leukocytes residing in the borders of the CNS are engaged in a continuous dialogue. As part of this dialogue, the parenchyma "informs" the leukocytes of its status and its needs through toxic agents that enter the CSF. In parallel, the leukocytes secrete cytokines that are required to neutralize the toxicity (Fig. 2). If this dialogue is interrupted, then local detoxifying mechanisms are recruited to an extended degree. Such destruction can occur as a normal part of aging, or prematurely under disease conditions, immune deficiency or stress (Preston, 2001; Redzic et al., 2005; Perez-Gracia et al., 2009; Ron-Harel and Schwartz, 2009).

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