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Review

Immune Activation in Brain Aging and Neurodegeneration: Too Much or Too Little?

Kurt M. Lucin[1,2] and Tony Wyss-Coray[1,2,*]
[1]Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA
[2]Geriatric Research, Education and Clinical Center, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304, USA
*Correspondence: twc@stanford.edu
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Until recently, the brain was studied almost exclusively by neuroscientists and the immune system by immunologists, fuelling the notion that these systems represented two isolated entities. However, as more data suggest an important role of the immune system in regulating the progression of brain aging and neurodegenerative disease, it has become clear that the crosstalk between these systems can no longer be ignored and a new interdisciplinary approach is necessary. A central question that emerges is whether immune and inflammatory pathways become hyperactivated with age and promote degeneration or whether insufficient immune responses, which fail to cope with age-related stress, may contribute to disease. We try to explore here the consequences of gain versus loss of function with an emphasis on microglia as sensors and effectors of immune function in the brain, and we discuss the potential role of the peripheral environment in neurodegenerative diseases.

Introduction

More than a half century ago, Peter Medawar noted a curious phenomenon. When heterologous tissues were transplanted into the CNS, he noticed that they were spared from immunological rejection (Medawar, 1948). This finding led him to speculate that the brain and immune system existed as two isolated systems. Until recently, this dogma was generally accepted, and brain immune responses were only studied in a few "immune-mediated" diseases. However, epidemiological studies revealing that long-term use of anti-inflammatory drugs reduces the risk for Alzheimer's (AD) and Parkinson's disease (PD) by roughly half hinted at a role for inflammation in classical age-related neurodegeneration (Chen et al., 2005; McGeer et al., 1996; Vlad et al., 2008). Growing evidence now suggests that the brain and immune system are intricately connected and engage in significant crosstalk to maintain homeostasis. Indeed, immune cells and mediators are routinely found in the CNS under normal and pathological states, while neurons are capable of interacting with and regulating immune cells. Neurodegenerative diseases also exhibit extensive microglial activation (the immune cells of the brain). Elegant studies combining mouse models that have various immune defects (developed by immunologists) with transgenic models for neurodegenerative diseases further implicate the immune system in disease progression by showing that lymphocytes play a role in PD, amyotrophic lateral sclerosis (ALS), and possibly AD. Interestingly, normal aging also exhibits immune activation and cell infiltration in the brain. Despite these commonalities, the role of the immune system in aging and neurodegenerative disease remains unclear. Here, we discuss some of the new and exciting findings that provide insight into how the immune system affects neurodegenerative disease and aging. Specifically, we will discuss how the immune system is activated and regulated in an aged and injured brain and whether impaired immune function may lead to the accumulation of protein aggregates in neurodegenerative disease.

Microglia: A Sensor of Brain Injury and Aging

A basic feature of all living organisms is the ability to detect potentially harmful stimuli and react accordingly. In the brain, glial cells constantly survey the microenvironment for noxious agents or injurious processes (Nimmerjahn et al., 2005). This is primarily done by microglia, a type of glial cell derived from myeloid precursors in the bone marrow that populate the CNS during development. Microglia are the resident immune cells of the brain and are endowed with numerous receptors capable of detecting physiological disturbances (see Figure 1). When neurons are injured as a result of aging or neurodegeneration, microglia become activated via the release of ATP, neurotransmitters, growth factors or cytokines, ion changes in the local environment, or loss of inhibitor molecules displayed by healthy neurons (Hanisch and Kettenmann, 2007). Microglia are also alerted that something is wrong when they encounter molecules not normally found in the healthy CNS, such as blood clotting factors, intracellular constituents released by necrotic cells (i.e., RNA, DNA), externalized phosphatidylserine on apoptotic cells, immunoglobulin-antigen complexes, opsonizing complement, abnormally folded proteins (i.e., protein aggregates), or pathogen-related structures (Hanisch and Kettenmann, 2007). Upon activation, microglia may proliferate and undergo a morphological transformation from a ramified to amoeboid appearance. Based on the activation stimuli, microglia are informed of the encountered problem and instructed to act in an appropriate manner and perform a defined task (e.g., clear apoptotic cells or abnormal proteins). If the disturbance is relatively minor (e.g., supporting a stressed neuron), microglia may secrete anti-inflammatory cytokines and supportive growth factors. If the disturbance poses a serious threat, such as a pathogen invasion, microglia may release toxic factors to kill the pathogen and recruit help by releasing proinflammatory cytokines (Figure 1). Depending on the environment in which microglia are activated, they can either take on a "classically

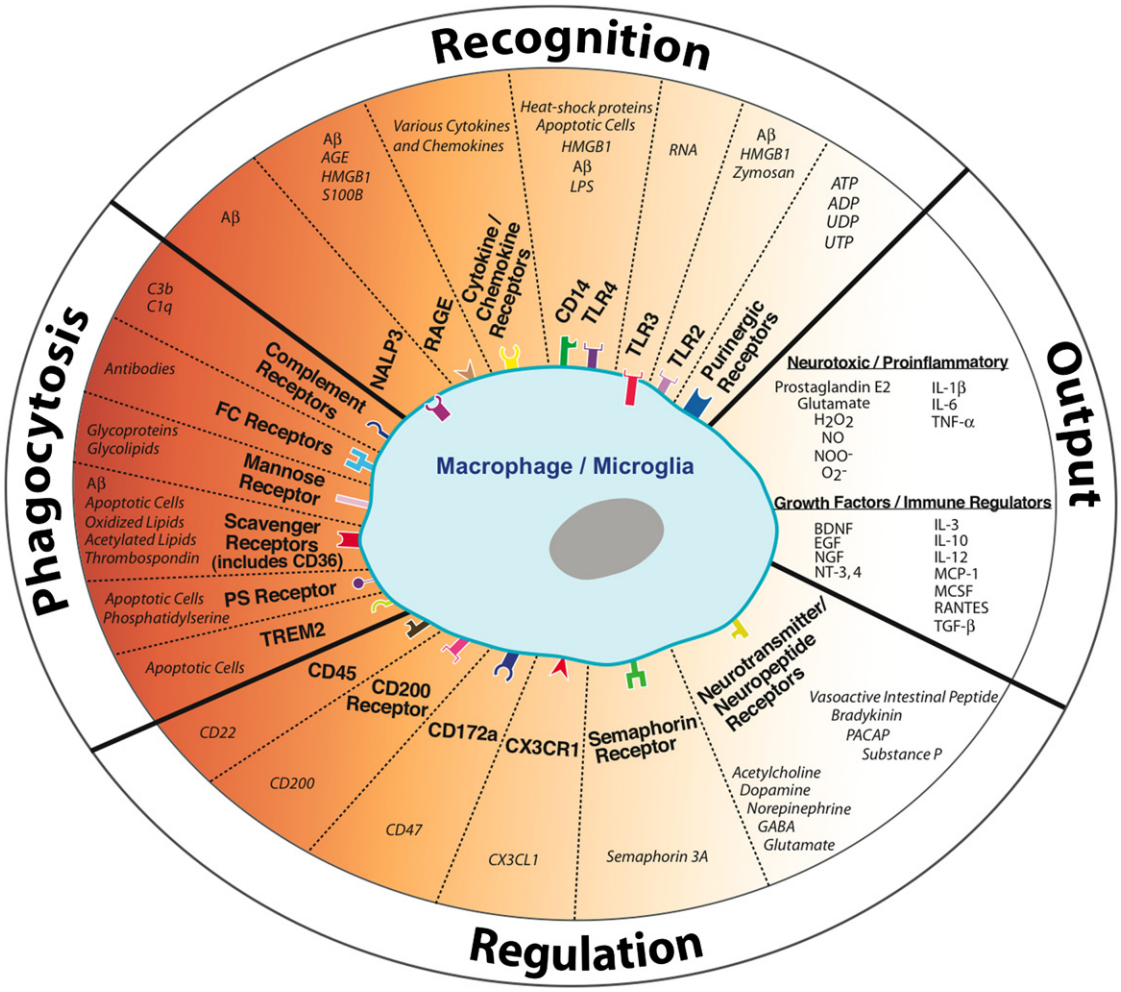

Figure 1. Regulation of Microglia/Macrophages in the CNS

Microglia/macrophages are activated following the stimulation of various recognition or phagocytic receptors. This activation state is subsequently controlled by neurons, which secrete or express numerous regulatory ligands. The end result of these interactions is the release of cytokines, neurotoxic substrates, and/or growth factors by microglia/macrophages or the activation of cellular pathways including phagocytosis. Aberrant function of these pathways can result in significant degeneration during aging or disease. For an extensive review of cytokines and chemokines recognized by microglia, refer to Hanisch (2002). Aβ, amyloid-β; ADP/ATP, adenosine di/triphosphate; AGE, advanced glycation end product; BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor; GABA, gamma-aminobutyric acid; H_2O_2, hydrogen peroxide; HMGB1, high-mobility group box 1; IL-1β, interleukin 1β; LPS, lipopolysaccharide; MCP-1, monocyte chemotactic protein-1; MCSF, macrophage colony-stimulating factor; NGF, nerve growth factor; NO, nitric oxide; NOO^-, peroxynitrite; NT-3,4, neurotrophin-3,4; O_2^-, superoxide; PACAP, pituitary adenylate cyclase-activating peptide; PS, phosphatidylserine; RAGE, receptor for advanced glycation end products; RANTES, regulated upon activation, normal T cell expressed and secreted; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNFα, tumor necrosis factor-α; TREM2, triggering receptor expressed by myeloid cells-2; UDP/UTP, uridine di/triphosphate. Receptors displayed inside the cell represent intracellular receptors. Different receptor shapes are not meant to represent actual receptor structures.

activated" (also called M1) phenotype or an "alternatively activated" (also called M2) phenotype (Mantovani et al., 2004). M2 microglia are typically considered less inflammatory than M1 cells and are characterized by reduced nitric oxide production and increased anti-inflammatory cytokine production. Accordingly, microglial heterogeneity exists during neurodegenerative disease and may influence disease outcome (Colton et al., 2006; Maier et al., 2008). Given the continuum of potential microglial responses, how a given insult is interpreted can mean the difference between a beneficial outcome or a detrimental outcome if the response is either too aggressive or too passive.

PAMPs and DAMPs Sound the Alarm

In order to detect and interpret potential insults, the immune system has evolved an ingenious set of receptors that detect small molecular motifs consistently found on pathogens or factors associated with tissue damage. Detection of these ***exogenous*** pathogen-associated molecular patterns (PAMPs) or ***endogenous*** danger-associated molecular patterns (DAMPs) is accomplished by a vast array of highly conserved pattern-recognition receptors (Janeway and Medzhitov, 2002; Seong and Matzinger, 2004). While toll-like receptors (TLRs) have received the most attention for their ability to recognize both classes of these molecular patterns (see below), many other

receptors that recognize specific molecular patterns have been described (e.g., complement, mannose, scavenger, C-type lectin, nucleotide-binding oligomerization domain [Nod]-like [including NALP3 and NOD2], and retinoic acid-inducible gene I [RIG-I]-like helicase receptors) (Palm and Medzhitov, 2009). Additional receptors also exist that appear to selectively recognize DAMPs, including CD24 and receptor for advanced glycation end-products (RAGE) (Arancio et al., 2004; Chen et al., 2009).

To date, 13 TLRs have been described that collectively recognize various PAMPs essential for pathogen survival (reviewed by Iwasaki and Medzhitov, 2004). TLRs are expressed on a variety of immune cells, including macrophages, dendritic cells, B cells, specific types of T cells, and even nonimmune cells such as epithelial cells, fibroblasts, and neurons. Stimulation of TLRs induces a well-characterized signaling cascade, culminating in the activation of nuclear factor κB and subsequent transcriptional activation of numerous proinflammatory genes, encoding cytokines, chemokines, complement proteins, enzymes (such as cyclooxygenase 2 and the inducible form of nitric oxide synthase), adhesion molecules, and immune receptors (Nguyen et al., 2002). In the face of an invading pathogen, these factors allow for a robust and coordinated immune response capable of eradicating infectious pathogens. While this approach is highly effective for eliminating pathogens, it comes at the expense of extensive bystander injury. Indeed, CNS microinjections of the TLR 2 or 4 ligands zymosan and LPS, respectively, cause robust glial activation and elicit substantial neurodegeneration (Lehnardt et al., 2003; Popovich et al., 2002). This becomes increasingly problematic when one considers that TLRs can also be engaged by DAMP-containing molecules released by CNS trauma or disease (e.g., heat-shock proteins [HSPs], high-mobility-group box protein 1 [HMGB1], fibrinogen, hypomethylated mammalian DNA, and RNA released from necrotic cells) (Kariko et al., 2004; Leadbetter et al., 2002; Ohashi et al., 2000; Smiley et al., 2001; Viglianti et al., 2003). In support of this, TLR4-deficient mice have smaller infarct volumes and better functional outcomes than control mice in a sterile model of experimental stroke (Caso et al., 2007). One explanation for this finding is that HSP60, a molecule released from CNS cells undergoing necrotic or apoptotic cell death, activates microglia via TLR4 and causes enhanced nitric oxide production and neuronal cell death (Lehnardt et al., 2008). Interestingly, TLR2 and -4 are upregulated on cerebral cortical neurons in response to ischemia/reperfusion injury, and their absence protects primary neuron cultures from energy-deprivation-induced cell death (Tang et al., 2007). Given these observations, it is tempting to speculate that the concerted increase in expression of multiple TLRs in the aging brain (Berchtold et al., 2008; Letiembre et al., 2007) may generate a hypersensitive state of glia and neurons and thus magnify potential bystander injury. Exactly how neuronal TLRs promote neurodegeneration and the identity of their ligands is currently unclear. Additional studies are required to elucidate these mechanisms using more precise neuron-specific TLR-deficient mice.

While ischemia and subsequent necrosis may initiate neuroinflammation and provoke further neurodegeneration in models of acute neurological disease and trauma, they are unlikely to play a role in chronic neurodegenerative disorders where necrotic conditions are uncommon. Instead, abnormal protein assemblies can function as a possible trigger for cellular stress and neuroinflammation. Most neurodegenerative disorders are associated with the accumulation of abnormal protein assemblies (proteopathies) (Orr and Zoghbi, 2000; Sherman and Goldberg, 2001; Walker and LeVine, 2000), some of which result from specific genetic mutations. A common feature of these abnormal protein aggregates, which may occur inside cells or in the extracellular space, is the existence of β sheets, as detected by staining with Congo red or related dyes and referred to as amyloid. Interestingly, bacteria produce similar amyloidogenic aggregates on their cell surface that bind Congo red (Chapman et al., 2002; Hammer et al., 2007). This begs the question of whether amyloid structures act as PAMPs and are interpreted as invading pathogens that elicit an aggressive neurotoxic response. In line with this hypothesis, Aβ is known to bind the TLR4 coreceptor CD14 (Fassbender et al., 2004; Liu et al., 2005) and can trigger microglia to secrete nitric oxide, interleukin (IL)-6, and other neurotoxic factors (Walter et al., 2007). Consistent with this, levels of tumor necrosis factor (TNF)-α and macrophage inflammatory protein (MIP)-1β are significantly higher in the brains of AD mice with wild-type TLR4 than their mutant TLR4 AD counterparts (Jin et al., 2008). On the other hand, TLR-mediated activation of microglia may also aid in the clearance of Aβ. Studies in AD mouse models with mutant TLR2 or TLR4 suggest that deficiencies in TLR signaling causes cognitive impairments with a concomitant increase in Aβ deposition (Richard et al., 2008; Tahara et al., 2006). Likewise, acute administration of the TLR4 ligand LPS can promote Aβ clearance (DiCarlo et al., 2001), and studies in mouse models of ALS suggest that TLR signaling is protective in disease progression (Kang and Rivest, 2007). Whether these receptors normally exacerbate neurodegeneration or guide the clearance of protein aggregates is still largely unknown and many studies, particularly with Aβ, do not consider the aggregation state of the peptide. It is thus likely that different receptors will be engaged by monomers, oligomers, or fibrillar assemblies of Aβ and that other amyloidogenic peptides may elicit different types of responses in microglia (and other cells).

The Complex Life of Complement

Complement proteins represent another line of defense in recognizing PAMPs and DAMPs and act as secreted pattern-recognition receptors. Using a collagen-like receptor binding domain and multiple globular domains, complement component C1 binds molecular patterns on microbes, dying cells, and abnormal protein aggregates (Tenner, 1999). Although the liver is the major source of complement, neurons and glia can make nearly all of the 30 different proteins involved in the complement cascade. During AD (Akiyama et al., 2000; Gasque et al., 2000), HD (Singhrao, 1999), PD (Yamada et al., 1992), and prion disease (Dandoy-Dron et al., 1998), levels of various complement components increase. An increase in complement proteins C1q, mannose binding lectin, and C3 can all initiate neuroinflammatory processes by activating inflammatory cells, promoting their migration, upregulating phagocytosis, and facilitating lysis by the membrane attack complex (Holers, 1996; Song et al., 2000). In AD, complement products, including the membrane

attack complex, colocalize with amyloid plaques and tangle-bearing neurons (Webster et al., 1997). APP mouse models where C3 activation is inhibited, via overexpressing soluble complement receptor-related protein y (sCrry), find an increase in Aβ deposition and an accumulation of degenerating neurons (Wyss-Coray et al., 2002). In support of this, APP mice with a complete knockout of C3 also show increased Aβ and neuronal degeneration, accompanied by changes in microglial activation (Maier et al., 2008). These data suggest that C3 may work with microglia to effectively clear Aβ. Alternatively, C3 may act in the periphery to clear circulating Aβ by creating a peripheral sink, as previously proposed (DeMattos et al., 2001). Indeed, studies show that Aβ binds to complement receptor 1 on red blood cells in a C3-dependent manner and that AD patients in their earliest stages have significantly less Aβ bound to red blood cells (Rogers et al., 2006). Because the genetic manipulations were systemic in the previously mentioned studies (Wyss-Coray et al., 2002; Maier et al., 2008), this theory cannot be ruled out. Studies using sCrry under the GFAP or hepatocyte-specific transthyretin promoters could shed light on this question.

But again, complement proteins like other immune factors can have detrimental effects. APP mice lacking complement C1q had less neuronal damage than complement-sufficient mice, suggesting a role for C1q in neuronal integrity (Fonseca et al., 2004). Indeed, C1q and C3 have recently been shown to mediate synaptic pruning during development and in a model of glaucoma, opening the possibility that complement factors may contribute to aberrant elimination of synapses in neurodegenerative diseases (Stevens et al., 2007).

Microglia in Neurodegeneration: Repairman or Reckless Killer?

Maybe 90% of published articles on microglia in neurodegeneration link activation of these cells with proinflammatory cytokine production and execution of neuronal cell death. Thus, microglia are thought to be responsible for killing dopaminergic cells in PD (Mount et al., 2007) and forebrain neurons in AD, and they have been shown to contribute to neurodegeneration in SOD1 transgenic mouse models for ALS (Boillee et al., 2006). Microglial-derived factors capable of inducing neuron death are numerous and range from reactive oxygen species to proinflammatory cytokines (see Figure 1). TNF-α is one such factor that has received much attention because of its ability to promote PD progression (McCoy et al., 2006), while TNF receptor 1 knockout protects against AD- and PD-like disease in mice (He et al., 2007; Sriram et al., 2002). Inhibiting the neurotoxic potential of proinflammatory cytokines is also likely to contribute to the beneficial effects of NSAIDs on neurodegenerative diseases. Interestingly, ablating reactive microglia by 50% in a model of ALS has no effect on motor neuron degeneration, suggesting that deleterious microglial function may be context dependent (Gowing et al., 2008). Clearly in most cases hyperactivated microglia can be deleterious and must be regulated to prevent neuronal damage.

Keeping the Beast in Check: Neurons as Tamers of Microglia

Interestingly, the brain has evolved various safety measures to keep microglia in check (Figure 1). These mechanisms allow neurons to downregulate microglial function until neuronal health is compromised. For example, CD200 is a membrane glycoprotein expressed by neurons that interacts with its cognate receptor on microglia (CD200R) to deliver regulatory signals. When mice are genetically deficient in CD200, microglial reactivity is enhanced under normal and pathological conditions (i.e., EAE and facial nerve axotomy) (Hoek et al., 2000). Similar to CD200, the integrin-associated protein CD47 is expressed by neurons and when bound to its receptor on microglia (SIRPα; CD172a) inhibits TNF-α release and phagocytosis (Oldenborg et al., 2001; Smith et al., 2003). These regulatory molecules appear to be relevant to humans as well, given that both CD47 and CD200 are downregulated in the center of chronic active and inactive human MS lesions, suggesting a possible role in propagating microglial activation and proinflammatory cytokine release (Koning et al., 2007). Fractalkine (CX3CL1) is another ligand expressed by neurons that restricts microglial activation when bound to its receptor (CX3CR1) (Cardona et al., 2006). This ligand-receptor interaction is absent when neurons die or are damaged, resulting in hyperresponsive microglia. Accordingly, in mouse models of Parkinson's disease or ALS, lack of CX3CR1 leads to extensive neuronal cell loss (Cardona et al., 2006). Microglia also express CD14, CD36, and phosphatidylserine receptors that, when bound to specific ligands on apoptotic cells (i.e., neurons), trigger inhibitory intracellular signals that reduce nitric oxide and proinflammatory cytokine release, while concomitantly increasing anti-inflammatory cytokine production (Savill et al., 2002). Triggering receptor expressed by myeloid cells-2 (TREM2) is an additional receptor on microglia that promotes phagocytosis and retards inflammation upon binding unknown ligands on apoptotic cells (Hsieh et al., 2009). When neurons are stressed, they can secrete semaphorin 3A and induce apoptosis of activated microglia, which express upregulated levels of the semaphorin receptors plexin-A1 and neuropilin-1 (Majed et al., 2006). This response is thought to protect neurons from further microglia-mediated damage. Neurons also release the anti-inflammatory neuropeptide CD22 from their nerve terminals, which regulates microglia activation and proinflammatory cytokine production via its receptor CD45 (Mott et al., 2004). Various secreted neurotransmitters have also shown similar modulatory effects on microglia (Pocock and Kettenmann, 2007), and suppressing spontaneous neuronal activity increases immune reactivity (Neumann et al., 1996). It should be noted that these regulatory mechanisms may prevent damage, but the extent to which they inhibit inherent repair mechanisms is unclear. More sophisticated tetracycline-inducible promoters or pharmacological tools are required to address whether intervening with these processes at defined time points may provide significant therapeutic benefit.

Do Changes in Brain and Microglial Function with Age Promote Neurodegeneration?

Although microglia are typically regarded as robust proinflammatory minutemen, microglia existing within an aging environment may be a different beast altogether. Aging is the strongest risk factor for neurodegenerative diseases, and while aging is not considered a disease, it results in a significant increase in glial activation (see Figure 2), complement factors, inflammatory

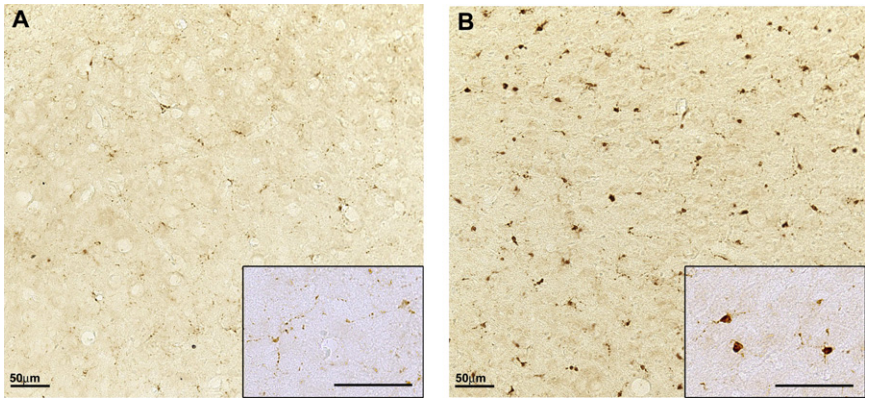

Figure 2. Increased Microglial Activation in the Aged Brain
Immunostaining for the endosomal/lysosomal enzyme CD68, a marker of the microglia/macrophage lineage, shows a prominent increase in the neocortex of 24-month-old C57BL/6 mouse (B) compared with a 6-month-old mouse (A), consistent with increased microglial activation in aged brains. Inserts show individual microglia under higher magnification where hypertrophied cell bodies are evident in aged brains (compare insert A to B). Scale bars represent 50 μm under 20× or 40× magnification.

mediators, and brain atrophy (Lu et al., 2004; Streit et al., 2008; West et al., 1994). Microarrays of aged human and mouse brains extend these findings by showing that genes related to cellular stress and inflammation increase with age while genes related to synaptic function/transport, growth factors, and trophic support decrease (Lee et al., 2000; Lu et al., 2004). These global changes paint a bleak picture of the aged brain and suggest that neurons encounter increased challenges with age but receive reduced support. To make matters worse, neurogenesis also decreases with age—possibly as a result of factors secreted by activated microglia (i.e., IL-6) (reviewed in detail in Carpentier and Palmer [2009], this issue of *Neuron*; also see Monje et al., 2003). It is unclear why inflammation increases with age, but genetic studies suggest an important role of DNA damage caused by increased reactive oxygen species (Lu et al., 2004). Also unclear is to what extent aging affects the responsiveness of microglia or their potential to contribute to neuronal loss. Despite morphological and phenotypic changes that indicate microglial activation (Figure 2), it has been proposed that microglia may actually become dysfunctional and enter a senescent state with age (Streit et al., 2008). Such a state may cause microglia to secrete diminished levels of neurotrophic factors and to downregulate phagocytic function. This, coupled with increased secretion of inflammatory mediators, may lead to neuronal loss and inefficient clearance of toxic protein aggregates in neurodegenerative disease.

Impaired Trash Removal as a Risk Factor for Neurodegeneration?

The accumulation of protein aggregates in neurodegenerative diseases may occur from enhanced production of abnormal proteins or abnormal folding. Alternatively, accumulating protein aggregates may result from insufficient clearance. Recent evidence suggests that impaired autophagy is one mechanism that influences the clearance of protein aggregates and neurodegenerative disease pathogenesis (Pickford et al., 2008; Ravikumar et al., 2004). Autophagy (also known as macroautophagy) is the major pathway involved in the degradation of long-lived proteins (Klionsky and Emr, 2000). Autophagy is highly conserved in all species and cell types studied thus far. It is initiated by the formation of a cup-shaped isolation membrane around cytosolic components, which eventually encloses to form a double membrane vesicle (two bilayered membranes) (Wang and Klionsky, 2003). This autophagosome undergoes several microtubule-dependent maturation events before eventually fusing with lysosomes, where cytosolic contents are degraded (Berg et al., 1998). Autophagy is impaired in AD (Nixon et al., 2005) and is implicated in the clearance of protein aggregates associated with AD, PD, and HD (Pickford et al., 2008; Ravikumar et al., 2004; Webb et al., 2003). The exact mechanism by which protein aggregates are targeted during autophagy is unclear. One possible link for intracellular aggregates is the protein sequestosome 1 (SQSTM1, also known as p62), which binds both ubiquitin (protein aggregates are often polyubiquitinated) and the autophagosome protein MAP1LC3 (Pankiv et al., 2007). Also unclear is which cell type(s) are influenced by autophagy to regulate levels of protein aggregates. Given that many protein aggregates have an intraneuronal component that may precede extracellular deposition, neurons are likely a target of critical importance (for further review see Jaeger and Wyss-Coray, 2009). However, emerging evidence also indicates a link between autophagy and phagocytic function in microglia/macrophages (see below).

Extracellular clearance of debris is classically attributed to phagocytes such as the peripheral macrophage, which literally means "big eater" (derived from the Greek words makros "large" + phagein "eat"). These bone-marrow-derived cells accomplish clearance of debris via phagocytosis, a receptor-mediated process whereby engagement of specific receptors (e.g., PAMPs and DAMPs) triggers actin polymerization and engulfment into specialized vesicles called phagosomes. The phagosome is internalized and fuses with lysosomes where its contents are degraded. Evidence for autophagy interacting with phagocytosis was first discovered in studies utilizing *Mycobacterium tuberculosis*, which is a bacterium that persists in macrophage phagosomes by interfering with phagolysosome biogenesis (Gutierrez et al., 2004). Promoting autophagy in infected macrophages caused colocalization of the autophagy effectors LC3 with phagosomes and suppressed intracellular survival of mycobacteria (Gutierrez et al., 2004). Using more elegant methods to establish a connection between autophagy and phagocytosis in macrophages, proteomic analysis on the membrane fraction of latex-bead-containing phagosomes revealed the presence of LC3-II (Shui et al., 2008). Recent studies have strengthened this connection and additionally suggested that TLR-2 and -4 stimulation during macrophage

phagocytosis recruits LC3 to the phagosome membrane and assists in phagosome maturation (Sanjuan et al., 2007). It is now clear that various TLR ligands activate autophagy in macrophages (Delgado et al., 2008; Xu et al., 2007). Because TLRs can recognize pathogenic protein aggregates, collaboration between autophagy and phagocytosis may represent a newly recognized innate defense mechanism for eliminating abnormal protein aggregates. Therefore, deficits in autophagy, as seen in AD (Pickford et al., 2008), may actually have mutually exclusive effects on the clearance of intraneuronal aggregates by macroautophagy and extracellular aggregates by phagocytosis.

While this newly emerging collaboration between autophagy and phagocytosis is intriguing in the context of neurodegeneration, triggering classical phagocytosis in the CNS may also directly improve clearance of aggregates. During acute CNS injury, when the blood-brain barrier (BBB) is severely compromised and robust inflammation is elicited, blood-derived macrophages (known as monocytes) infiltrate the CNS and contribute to the pathological sequelae. Unfortunately, CNS-resident microglia and blood-derived monocytes entering the CNS take on similar morphological and phenotypic profiles, currently making the two cell populations almost indistinguishable. Chronic neurodegenerative disease (e.g., AD and PD) causes only subtle inflammation, and the contribution of blood-derived monocytes is controversial (see below). However, what is clear is that microglia and astrocytes are activated and produce an array of inflammatory mediators, while upregulating phagocytic activity (Aldskogius et al., 1999). Using in vivo multiphoton imaging, the specific kinetics of this response were recently revealed (Meyer-Luehmann et al., 2008). This study showed that Aβ plaques form rapidly within 24 hr and subsequently recruit activated microglia to the plaques within 1–2 days, dispelling previous notions that microglia may actually contribute to plaque formation. Instead, mounting evidence proves that microglia are capable of taking up Aβ. Indeed, amyloid fibrils have been detected in microglia cultured with Aβ and in AD brains (Frackowiak et al., 1992; Wegiel and Wisniewski, 1990). Increased microglial activation is also associated with reduced Aβ accumulation in human APP transgenic mice (Herber et al., 2004; Wilcock et al., 2004; Wyss-Coray et al., 2001).

Microglia are capable of taking up soluble Aβ via macropinocytosis (Mandrekar et al., 2009) and insoluble Aβ aggregates via phagocytosis. Following internalization, soluble Aβ appears to be readily degraded (Mandrekar et al., 2009), but dense insoluble aggregates may be more difficult for microglia to handle. Indeed, mouse microglia phagocytose large amounts of Aβ in vitro, but the majority of internalized Aβ is undegraded 72 hr after uptake (Paresce et al., 1997). In fact, when cultured with primary dog microglia, undigested Aβ (obtained from human AD patients) can be detected in phagosomes for up to 19 days (Frackowiak et al., 1992). However, not all proteins ingested by microglia universally experience impaired degradation. 70%–80% of internalized nonamyloid proteins (e.g., acetylated low-density lipoprotein or alpha2-macroglobulin) are degraded and released by microglia within 4 hr (Paresce et al., 1997). Undegraded Aβ is also released by microglia (Chung et al., 1999), suggesting that detection of Aβ within microglia may not prove its clearance. As a result, the effectiveness of microglia in amyloid clearance has come into question. Recent studies suggest that microglia are ineffective during neurodegenerative disease because they are ill equipped for the job. In a mouse model of AD, old PS1-APP mice have a 2- to 5-fold decrease in Aβ-binding scavenger receptors and Aβ-degrading enzymes, despite increases in proinflammatory cytokines (Hickman et al., 2008). When AD mice are treated with the anti-inflammatory drug minocycline, microglial activation and IL-6 levels are reduced, but levels of various Aβ species are unchanged (Fan et al., 2007). Despite a lack of Aβ clearance, minocycline-treated mice show a significant improvement in behavioral performance. Thus, microglia may only play a minor role in amyloid clearance, but may become activated by protein aggregates and contribute to secondary degeneration via release of neurotoxic factors. The consequences and, most importantly, the significance of microglial interactions with Aβ in AD remain unclear. This is in part due to the plethora of different experimental settings used in published studies, including different types and sources of Aβ assemblies (which may recruit different receptors on microglia), different cell types (neonatal versus adult primary cells, or cell lines), and cell culture versus in vivo. To develop disease-relevant findings, putative Aβ receptors need to be tested in loss- and gain-of-function animal models and ideally in more than one AD animal model.

Cerebral Infiltration of Immune Cells in Neurodegeneration

In models where effective amyloid clearance is observed, it has recently been attributed to infiltrating monocytes or perivascular macrophages, which seem to readily degrade amyloid (Hawkes and McLaurin, 2009; Majumdar et al., 2008). This disparity may be explained by microglial lysosomes being less acidic than macrophage lysosomes, resulting in reduced activity of lysosomal enzymes (Majumdar et al., 2007). Indeed, treating microglia with macrophage colony stimulating factor (M-CSF) acidifies microglial lysosomes to levels comparable to macrophages and facilitates Aβ degradation (Majumdar et al., 2007). Although CNS-infiltrating monocytes appear beneficial for amyloid clearance, their role in human neurodegenerative disease remains unclear. This has been a source of controversy because initial studies implicating blood-derived monocytes in promoting Aβ clearance used a bone marrow irradiation model to track GFP monocytes into the diseased brain (Simard et al., 2006). This model is not ideal because irradiation itself may damage the BBB and activate the peripheral immune system, thus augmenting cellular infiltration. More recent studies using parabiosis (a technique that allows shared vasculature between two mice) showed that when wild-type mice are joined with GFP mice, GFP monocytes do not enter the brain under normal conditions or after CNS insult (Ajami et al., 2007). Only when mice encounter irradiation and bone marrow transplants do bone-marrow-derived monocytes infiltrate the brain. A complementary study also showed that bone-marrow-derived cells do not contribute to microglial populations unless the brain is irradiated (Mildner et al., 2007). This study provided further insight by characterizing a specific bone-marrow-derived cell population that infiltrates the brain after irradiation (Ly-6C^{hi} CCR2^{+} cells) and identified the importance of the chemokine receptor CCR2 in this

Table 1. Cellular Infiltration in Neurological Disease

Disease	Protein Aggregates	Infiltrating Cell Type	Beneficial or Detrimental	Experimental Model	Irradiation	Reference
ALS	mSOD1	monocytes	role unknown	mSOD1	yes	Kang and Rivest, 2007
		CD4+ T cells	+	mSOD1	no	Beers et al., 2008; Chiu et al., 2008
				human	n/a	Engelhardt et al., 1993
		CD8+ T cells	role unknown	mSOD1	no	Beers et al., 2008; Chiu et al., 2008
				human	n/a	Engelhardt et al., 1993
		NK cells	role unknown	mSOD1	no	Chiu et al., 2008
Alzheimer's Disease	Aβ, Tau	monocytes	+	App_{swe}/PS1, APP23	yes	Malm et al., 2005; Simard et al., 2006; Stalder et al., 2005
				Tg2576/TGFβ DNR	no	Town et al., 2008
		T cells	+	human	no	Rogers et al., 1988; Togo et al., 2002
				APP/IFN-γ		Monsonego et al., 2006
Huntington's Disease	Huntingtin	no reported studies found		Mhtt, human		
Parkinson's Disease	α-synuclein	monocytes	role unknown	MPTP	yes	Kokovay and Cunningham, 2005; Rodriguez et al., 2007
		CD4+ T cells	–	MPTP, human	no	Brochard et al, 2009; Kurkowska-Jastrzebska et al., 1999
		CD8+ T cells	role unknown	MPTP, human	no	Brochard et al., 2009; Kurkowska-Jastrzebska et al., 1999; McGeer et al., 1988
Prion Disease	Prp-amyloid	monocytes	role unknown	scrapie	yes	Priller et al., 2006; Williams et al., 1995
		T cells (CD4,8)	–	scrapie	no	Betmouni et al., 1996
				SCID + intracerebral ME7	yes	Blattler et al., 1997; Fraser et al., 1996
Aging	Reelin	T cells (CD4,8)	role unknown	aged Lewis rat, mice	no	Bradl et al., 2005; Knuesel et al., 2009

migration. In support of this concept, recent studies in a model of liver injury and peripheral inflammation suggested that fluorescently tagged monocytes can infiltrate the brain in a chemokine receptor CCR2-dependent manner (D'Mello et al., 2009). While such studies are technically challenging and need to be confirmed, they indicate that specific signaling pathways may allow the CNS to recruit monocytes from the periphery.

Additional studies indicate the chemokine CCL2 and its receptor CCR2 play a key role in regulating the infiltration of peripheral monocytes into the brain. Lack of CCR2 in mice results in reduced accumulation of microglia/monocytes in the brain and accelerates disease progression and Aβ deposition in a mouse model of AD (El Khoury et al., 2007). Because microglia from *CCR2*$^{-/-}$ mice do not exhibit aberrant proliferation (El Khoury et al., 2007), it was postulated that changes in microglia accumulation are a consequence of monocyte infiltration. Conversely, overexpressing CCL2 in the brain results in increased microglial accumulation (Yamamoto et al., 2005). However, overexpressing CCL2 also results in increased Aβ accumulation, which may be due to a prominent increase in mouse APOE (Yamamoto et al., 2005), a factor known to independently enhance Aβ deposition (Bales et al., 1999). Recent studies also suggest that infiltrating monocytes may originate from a subpopulation of CD11c monocytes when TGFβ signaling is impaired (Town et al., 2008). These cells appear to infiltrate and clear Aβ in a mouse model of AD (Town et al., 2008). While CD11c-expressing cells may indeed come from the periphery, recent reports show that CD11c microglia exist within the CNS under pathological and nonpathological conditions and may provide a pool for endogenous expansion in the absence of TGFβ signaling (Bulloch et al., 2008; Chiu et al., 2008).

In summary, flow cytometry has been used to describe several profiles, including $CD45^{high}CD11b^{+}$, $Ly\text{-}6C^{high}CCR2^{+}$, and $CD45^{+}CD11b^{+}CD11c^{+}$ (Mildner et al., 2007; Sedgwick et al., 1991; Town et al., 2008), which might identify monocytes that have recently infiltrated the brain. However, because microenvironmental changes in the CNS during an insult may alter expression profiles of microglia, resulting in profiles that resemble peripheral monocytes (Ponomarev et al., 2005), there is still doubt about the extent of monocyte recruitment into the CNS and the role these cells play in disease. Genetic models that prevent monocyte trafficking (e.g., P-selectin and α4 integrin knockouts; D'Mello et al., 2009; Kerfoot et al., 2006) might offer an opportunity to better define the role of resident microglia versus infiltrating monocytes in neurodegenerative disease models.

While this debate over monocytes infiltrating the brain continues, various other peripheral immune cells are clearly present during neurodegenerative disease (see Table 1). Maybe most surprisingly, T cells have been detected in nearly all neurodegenerative diseases studied, albeit in small numbers (see Table 1). And while these cells are seen as the culprit in diseases such as MS, new data in chronic neurodegeneration paint a more complex picture. Using a series of sophisticated genetic studies, three independent groups showed recently in ALS models that

mSOD1 mice lacking T cells show accelerated motorneuron disease while adoptive transfer of T cells ameliorated disease (Banerjee et al., 2008; Beers et al., 2008; Chiu et al., 2008). Meanwhile, in a mouse model of Parkinson's disease, dopaminergic cell death is markedly attenuated in the absence of T cells (Brochard et al., 2009). Similarly, mice lacking T and B cells are resistant to prion disease following intraperitoneal or intracerebral ME7 scrapie injection (Fraser et al., 1996). In this model, immune cells may cause degeneration, but may also be responsible for replication and transfer of the prion particles to the CNS (Blattler et al., 1997; Fraser et al., 1996). Interestingly, even if immune cells do not directly access CNS parenchyma, new studies suggest that T cells and polymorphonuclear leukocytes may promote seizures and subsequent degeneration by binding to the luminal side of cerebral blood vessels (Fabene et al., 2008). Consequently, inhibiting leukocyte-vascular interactions via blocking or deleting vascular adhesion molecules markedly reduced seizures. While this concept is seemingly tangential to common neurodegenerative disease, the fact that AD mice and certain patients show underlying seizure activity lends relevance to the possibility of these mechanisms contributing to disease pathogenesis (Amatniek et al., 2006; Palop et al., 2007). Currently, it is unclear whether Aβ aberrantly excites the neurocircuitry or recruits immune cells to CNS vasculature where interactions promote seizures, but this could be experimentally tested using APP mice deficient in vascular adhesion molecules.

Soluble Immune Factors Allow Crosstalk between the Periphery and CNS

If peripheral immune cells can be mobilized to the CNS during neurodegenerative disease, the CNS and periphery must engage in crosstalk that likely involves soluble factors. As mentioned above, CCL2 may function as a chemoattractant for peripheral monocytes (El Khoury et al., 2007), but many other factors could participate in regulating interactions between CNS and periphery. Such communication could involve proteins classically assigned to the immune system, including acute phase proteins, complement, cytokines, and chemokines, although these communication factors can be the source or target of many other tissues, including the brain. Indeed, many classical immune regulatory factors are produced by glial cells or neurons in the CNS and increased during injury. On the other hand, neurodegenerative changes in the brain appear to be associated with changes in the peripheral immune system. For example, freshly isolated peripheral blood mononuclear cells (PBMCs) from AD patients produce higher levels of IL-1β, IL-6, and oncostatin M than cells from nondemented controls (Reale et al., 2005). Using more global approaches, microarray analysis of PBMCs and lymphocytes from AD patients show a prominent gene dysregulation when compared to age-matched controls (Fiala et al., 2007; Kalman et al., 2005; Maes et al., 2007). Similarly, changes in patterns of soluble immune mediators and other communication factors in the periphery have been linked to AD, HD, and PD and were used to predict disease progression (Bjorkqvist et al., 2008; Ray et al., 2007; Scherzer et al., 2007). For example, elevated IL-6 levels were observed in preclinical HD mutation carriers up to 16 years before the onset of motor abnormalities (Bjorkqvist et al., 2008), and changes in the levels of 18 cellular communication factors in plasma predicted AD progression several years prior to clinical manifestation (Ray et al., 2007). Indeed, some of these 18 proteins have been linked mechanistically to AD or AD-like disease in mice, although others may be unrelated or false-positive findings. Overall, whether changes in immune function or expression of soluble mediators in the periphery affect neurodegeneration is still unclear. However, expanding the search for changes in cellular communication factors (which we dubbed the cellular communicome) in neurodegenerative disease to hundreds of proteins and increasing the number of patient samples could provide support for systemic dysregulation of biological pathways. If successful, proteins or biological pathways, which change as a result of neurodegeneration, could become targets for treatments, and groups of proteins might be used as diagnostic signatures and for disease therapy monitoring.

Currently, it is unknown whether altered peripheral communication factors in neurodegenerative disease are actively produced in the periphery, derived from the CNS, or both. It is also unclear whether these changes in peripheral immune factors are merely a correlate of CNS degeneration or actually impact disease progression. Emerging evidence is beginning to suggest the latter: that altering peripheral inflammation during neurodegenerative disease can significantly alter disease course (Perry et al., 2007). In support of this, studies show that systemic inflammatory challenges in mouse models of ALS, optic nerve crush, PD, and prion disease lead to exaggerated CNS inflammation and a significant increase in neurodegeneration, culminating in accelerated disease progression (Cunningham et al., 2005; Frank-Cannon et al., 2008; Nguyen et al., 2004; Palin et al., 2008). Similarly, in humans with AD, systemic infections and elevated plasma levels of IL-1β are both associated with an increased rate of cognitive dysfunction (Holmes et al., 2003). Chronic systemic expression of IL-1β in mouse models of PD enhances CNS inflammation and neurodegeneration (Godoy et al., 2008). In light of these findings, it is tempting to speculate that chronic peripheral inflammation may accelerate neurodegenerative disease. This theory may explain the reported epidemiological benefits of NSAIDs in AD and PD (Chen et al., 2005; McGeer et al., 1996; Vlad et al., 2008), where individuals may have an underlying inflammatory condition, but the lack of a beneficial effect in clinical trials where individuals with ancillary inflammatory conditions are excluded. If true, determining which types of chronic inflammation (i.e., arthritis, inflammatory bowel disease, infections, etc.) exacerbate neurodegenerative disease and finding effective treatments for these disorders will be critical for reducing overall disease progression.

Aside from intercellular communication factors, antibodies have also recently received much attention as peripheral immune molecules with a possible role in AD and other neurodegenerative diseases. Stimulating the production of Aβ antibodies by active immunization with synthetic Aβ (Schenk et al., 1999) or administering monoclonal Aβ antibodies (DeMattos et al., 2001; Levites et al., 2006) is being actively pursued as a potential treatment for AD and is discussed in the accompanying review by Yong and Rivest 2009 ([this issue of *Neuron*]). Interestingly, antibodies against Aβ occur naturally in blood and CSF in free form or in complex with Aβ, both in AD patients and healthy

individuals (reviewed in Szabo et al., 2008). Although titers of these antibodies are low, naturally occurring antibodies recognizing known toxic oligomeric Aβ and amyloidogenic non-Aβ species are abundant in healthy humans and nonhuman primates and decrease with age and advancing AD (Britschgi et al., 2009). Plasma IgGs are capable of reducing some of Aβ's neurotoxicity, and plasma Aβ antibodies may facilitate the clearance of Aβ, but more studies are necessary to understand the role of these antibodies in vivo.

Summary

The past few years have generated new links between the brain and immune system at a fervent pace and to a growing number of neuroscientists the names of immune molecules have become familiar, if not interesting. Given that many of these new links between the CNS and immune system were unexpected, neuroscientists and immunologists should take a humble step back and consider the factors they study (e.g., neurotransmitters or cytokines) as just that—factors in a complex organism that function based on their sequence and structure, not their anointed "immune" or "neuro" classification. Indeed, emerging studies highlighting the role of "immune molecules" such as complement and class I major histocompatibility complex in CNS development and plasticity (Huh et al., 2000; Stevens et al., 2007; and see review article in this issue by Boulanger [2009]) or "CNS factors" such as neurotransmitters in shaping immune function (Pocock and Kettenmann, 2007) attest to the disregard of proteins for classification. Moreover, while there is clearly strong support for a role of classical inflammatory cytokines such as TNF-α in neurodegeneration and a toxic gain of function by microglia, there are exciting experiments involving immune activation in neurodegeneration that leave room for loss-of-function paradigms. Apart from vaccines, however, medicine has clearly been more successful in inhibiting the immune system rather than activating it, and caution must be taken when attempting to boost microglia or macrophage function. In the meantime, we need to understand the molecular changes in immune cell function that occur with normal healthy aging, be it in the brain or in the peripheral immune system.

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