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Inflammation in Neurodegenerative Disease—A Double-Edged Sword

Review

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Inflammation is a defense reaction against diverse insults, designed to remove noxious agents and to inhibit their detrimental effects. It consists of a dazzling array of molecular and cellular mechanisms and an intricate network of controls to keep them in check. In neurodegenerative diseases, inflammation may be triggered by the accumulation of proteins with abnormal conformations or by signals emanating from injured neurons. Given the multiple functions of many inflammatory factors, it has been difficult to pinpoint their roles in specific (patho)physiological situations. Studies of genetically modified mice and of molecular pathways in activated glia are beginning to shed light on this issue. Altered expression of different inflammatory factors can either promote or counteract neurodegenerative processes. Since many inflammatory responses are beneficial, directing and instructing the inflammatory machinery may be a better therapeutic objective than suppressing it.

More than a century ago, Elias Metchnikoff, one of the founders of cellular immunology, discovered that ameboid cells of starfish larvae can devour foreign objects and digest cellular debris, leading him to postulate that phagocytes are inflammatory cells with beneficial functions (Metchnikoff, 1884). This hypothesis was soon challenged by some of his contemporaries, who maintained that phagocytes are themselves the perpetrators of inflammatory disease (Tauber, 1992). Scientists today face a similar dilemma in trying to decipher the role of inflammatory responses in the degenerating central nervous system (CNS), since many of these responses might either promote or inhibit the neurodegenerative process (Figure 1).

Inflammation is an active defense reaction of multicellular organisms against diverse insults, designed to remove or inactivate noxious agents and to inhibit and reverse their detrimental effects. It typically consists of multiple components and should not be simply equated with the infiltration of tissues by blood-derived immune cells, since such infiltration only represents one particular type of inflammatory response. Inflammation can be triggered by invading microbes such as viruses and bacteria, as well as by injurious chemicals or physical insults. It can also be initiated from within the organism, for example, by diseases affecting the immune system or the nervous system. In neurodegenerative diseases, inflammation may be triggered by the accumulation of aggregated or otherwise modified proteins, by signals emanating from injured neurons, or by imbalances between pro- and antiinflammatory processes.

Inflammatory responses also recruit immune mechanisms, and a growing number of studies are discovering intriguing links between the immune system and the CNS. For example, various immune cells can traverse the blood-brain barrier, although the CNS is partially sheltered from immune surveillance. During CNS development, blood-derived monocytes populate the brain to form microglia, and activated lymphocytes can cross the intact blood-brain barrier even in adults (Hickey, 2001). Invading lymphocytes can attack target antigens in the CNS or produce growth factors that might protect neurons against degeneration (Schwartz et al., 1999; Hohlfeld et al., 2000). Immune molecules such as Thy-1, interleukins, and chemokines are expressed at high levels in neurons and may be involved in the communication of neurons with glial cells (Leyton et al., 2001; Allan and Rothwell, 2001). Molecules mediating specific antigen recognition by T lymphocytes, including major histocompatibility complex (MHC) class I and CD3ζ molecules, also have a role in activity-dependent remodeling and plasticity in the developing and mature mammalian CNS (Boulanger et al., 2001).

There are three common outcomes of inflammation. The offending agent or process is inactivated and the injury repaired. The host loses the battle and dies or suffers irreparable tissue damage. Neither the organism nor the injurious process prevails, resulting in a prolonged battle that provides fertile ground for the development of chronic inflammatory conditions. The last outcome may relate closely to neurodegenerative diseases, one of the greatest public health problems of this century (Cowan and Kandel, 2001).

In this Review, we will examine the role of inflammation in neurodegenerative diseases. First, we will discuss some of the CNS alterations that could trigger inflammatory responses in these conditions. Second, we will review the main components of inflammatory responses in the CNS, which include both innate and acquired immune mechanisms. Third, we will highlight how difficult it is to pinpoint the specific role of multifunctional inflammatory mediators in different pathophysiological situations. Fourth, we will discuss the potential of manipulating inflammatory responses as a therapeutic strategy in neurodegenerative disorders.

Triggers of Inflammation in Neurodegenerative Disease

Crucial to the activation of inflammatory responses in a tissue is the sensing by host defense mechanisms of a noxious agent or an injurious process. The ability to distinguish foreign from self and abnormal from normal is among the most fascinating aspects of inflammation in the CNS and elsewhere. A dazzling array of molecular and cellular mechanisms has evolved to carry out these tasks, and we are only beginning to understand the intricate network of controls that keep these systems in check.

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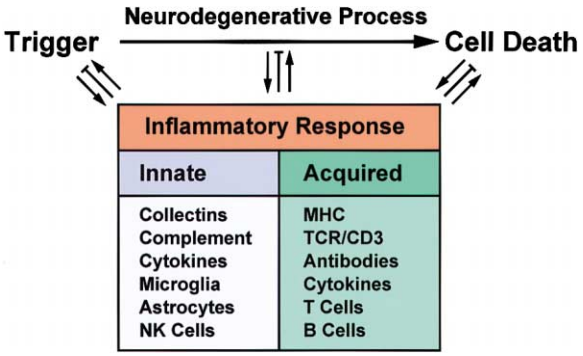

Figure 1. The Inflammatory Response as an Indicator and Potential Modulator of Neurodegeneration

Neurodegenerative processes culminate in cell death and are often associated with innate and acquired immune responses (partial listing). These inflammatory responses probably aim to remove the pathogenic trigger and inhibit the neurodegenerative process. However, uncontrolled or chronic inflammation may also promote this process. CD, cluster of differentiation; MHC, major histocompatibility complex; NK, natural killer; TCR, T cell receptor. ↓, stimulation; ⊥, inhibition.

Inflammation in neurodegenerative disorders might result from a number of causes: protein aggregates, accumulation of other abnormally modified cellular constituents, molecules released from or associated with injured neurons or synapses, and dysregulation of inflammatory control mechanisms (Figure 1). The resulting inflammatory responses may modulate neurodegenerative pathways in either a beneficial or a detrimental fashion.

Most neurodegenerative disorders are associated with the accumulation of abnormal protein assemblies (proteopathies) (Orr and Zoghbi, 2000; Walker and LeVine, 2000; Sherman and Goldberg, 2001), and increasing evidence suggests that such protein assemblies can be major triggers of cellular stress and neuroinflammation (Figure 2). The formation of abnormal protein assemblies in neurodegenerative diseases can result from genetic mutations in specific proteins. Mutations in the genes encoding human amyloid precursor protein (hAPP) or presenilins 1 or 2, which cause early-onset Alzheimer's disease (AD), result in abnormal proteolytic processing of hAPP, increasing the production and extracellular deposition of hAPP-derived amyloid β peptides (Aβ) (Selkoe, 2001). Mutations in the genes encoding the ubiquitin E3 ligase parkin or the de-ubiquinating enzyme Uchl1 lead to familial Parkinson's disease (PD) (Chung et al., 2001). In most other neurodegenerative diseases, mutations promote abnormal folding and aggregation of the mutated proteins themselves (Sherman and Goldberg, 2001). In AD, mutations account for only a small fraction of cases, suggesting that other factors must be responsible for the abnormal accumulation of Aβ seen in the vast majority of patients with this disease.

Whatever causes the extracellular deposition of Aβ in the form of amyloid plaques in sporadic AD cases, this process is clearly among the most notorious triggers of chronic inflammatory reactions in the CNS (Akiyama et al., 2000), and there is ample evidence from in vitro studies that Aβ aggregates can activate a variety of inflammatory pathways. For example, Aβ can trigger microglial activation by binding to the receptor for advanced glycation end products (RAGE) (Yan et al., 1999) or other scavenger receptors (Paresce et al., 1996; El Khoury et al., 1996), and at least some of these pathways seem to involve the CD40 signaling receptor (Tan et al., 1999). Aβ fibrils also bind to RAGE on neurons, causing cellular stress and the release of inflammatory factors (Yan et al., 1999). Aggregated Aβ can activate the complement system in vitro through the classical pathway by binding C1q and through the alternative pathway by binding C3b (Rogers et al., 1992; Webster et al., 1997a; Bradt et al., 1998). Complement was also activated by neurofibrillary tangle preparations isolated *postmortem* from human AD brains (Shen et al., 2001). Treatment of neurons with proteasome inhibitors elicited accumulation of ubiquinated proteins and increased neuronal production of cyclooxygenase (COX) 2 and proinflammatory prostaglandins (Rockwell et al., 2000), suggesting that the production of inflammatory mediators can be triggered not only by extracellular protein deposits but also by the intracellular accumulation of abnormal proteins.

Aging is associated with glial activation, increased production of inflammatory mediators, accumulation of modified proteins and lipids, and neuronal deficits (Masliah et al., 1993; West et al., 1994; Jucker and Ingram, 1997; Morgan et al., 1999). A comparison of 5- and 30-month-old mice revealed a prominent increase in the expression of many inflammatory and stress genes in the aged mice, including complement factors, glial activation markers, cyclophilin, and heat shock proteins (Lee et al., 2000). The precise causes of these aging-associated alterations are unknown, but there is evidence that reactive oxygen species may play an important role (Beckman and Ames, 1998; Prolla and Mattson, 2001). It remains uncertain to what extent the inflammatory changes associated with aging explain why aging is an important risk factor for all major neurodegenerative diseases.

Chronic inflammation might be maintained by cellular distress signals emanating from neurons that survive for prolonged periods despite the abnormal accumulation of proteins and significant injury to their presynaptic terminals or dendritic processes. Synaptic degeneration is indeed a prominent feature of neurodegenerative diseases and related transgenic models. For example, loss of synaptophysin-immunoreactive presynaptic terminals correlates well with cognitive decline in AD (DeKosky and Scheff, 1990; Terry et al., 1991) and develops in hAPP transgenic mice well before Aβ is deposited into extracellular amyloid plaques (Mucke et al., 2000). The accumulation of nonfibrillar oligomeric Aβ species (Klein et al., 2001) in or around presynaptic terminals might disrupt vesicle trafficking, transmitter release, and synaptic integrity. In addition, Aβ might disrupt axonal transport (Gunawardena and Goldstein, 2001), which would also interfere with the maintenance of synaptic contacts. Similar synaptic deficits could also contribute to PD (Masliah et al., 2000, 2001), since synapses are highly enriched with α-synuclein, the main component of the intraneuronal Lewy bodies found in this condition. In experimental models of nerve injury, degenerating synapses trigger the rapid activation of astrocytes and

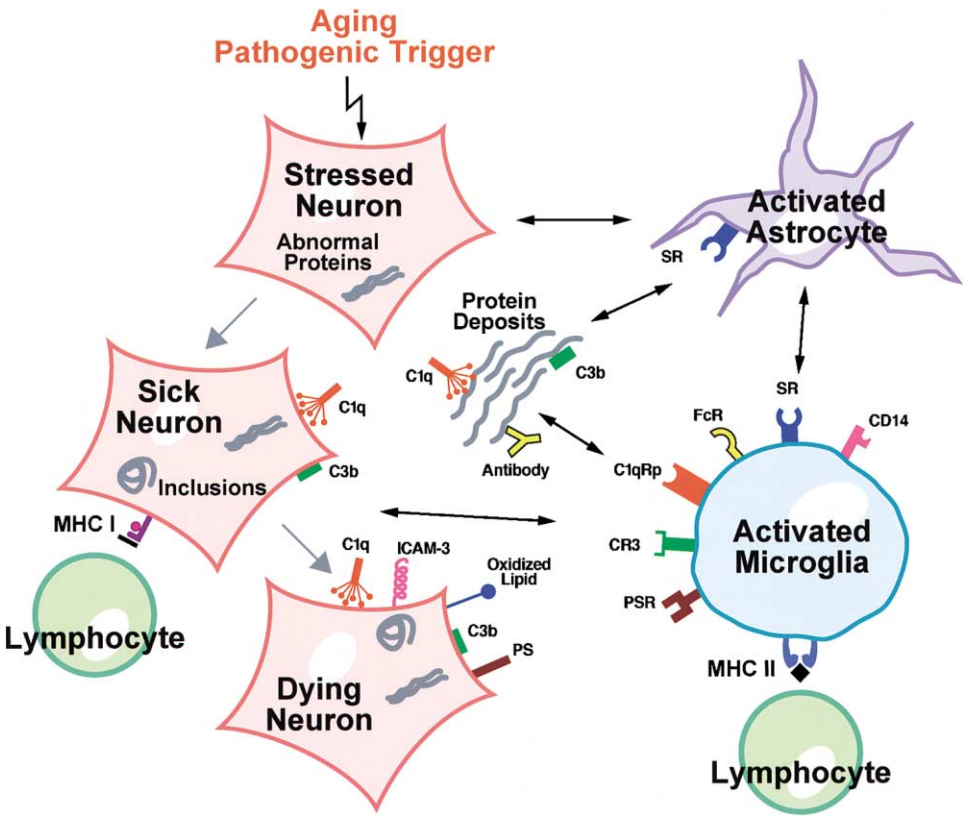

Figure 2. Some Components of the Inflammatory Response to CNS Degeneration

Pathogenic triggers, such as accumulation of abnormal proteins in cells or extracellular spaces, elicit cellular stress responses and can result in the progressive dysfunction and degeneration of neurons. Interactions indicated by arrows involve a large number of soluble factors. Cytokines and other mediators of the innate immune response are released by astrocytes and microglia to orchestrate defense mechanisms and initiate the removal or sequestration of the pathogenic triggers. A selection of molecules and receptors involved in the recognition of abnormal proteins and degenerating cells is illustrated. Colors are used to indicate interactions between ligands and receptors. Abnormal proteins and degenerating neurons are tagged by complement proteins such as C3b or C1q or by antibodies for recognition and phagocytosis by glial cells. Degenerating neurons may also be phagocytosed if they display intercellular adhesion molecule-3 (ICAM-3), phosphatidyl serine (PS), or oxidized lipids on their cell surface. Receptors on glial cells recognize these tags and initiate inflammatory responses. MHC molecules might display abnormal proteins with novel antigenic epitopes to lymphocytes, resulting in acquired immune responses. C1qRp, C1q receptor for phagocytosis; CR3, complement receptor 3; FcR, Fc receptor; PSR, phosphatidyl serine receptor; SR, scavenger receptor.

microglia and the release of inflammatory mediators (Aldskogius et al., 1999).

Degenerating cells can provoke inflammation until they are cleared by phagocytes. Whether the death of neurons and other CNS cells gives rise to inflammatory reactions may depend, at least in large part, on how they die. A particular type of programmed cell death, apoptosis, plays a key role in shaping the CNS during development. If executed effectively, apoptosis results in the uneventful removal of dying cells, with little or no inflammation (Sastry and Rao, 2000). Although apoptosis clearly occurs in neurodegenerative disorders, it remains uncertain whether it accounts for most of the neuronal loss and whether it can be executed flawlessly in these conditions (Cotman et al., 1999; Sperandio et al., 2000; Green and Beere, 2001; Raina et al., 2001).

A different type of cell death, necrosis, is almost always pathological and often triggers a prominent inflammatory reaction. Although necrotic cell death can occur in neurodegenerative disorders, there is typically much less evidence for it in these conditions than in more acute neurological diseases, such as stroke or viral encephalitis. There are also forms of cell death that combine aspects of apoptosis and necrosis but do not fit into either of these categories, including paraptosis (Sperandio et al., 2000) and abortosis (Raina et al., 2001). These forms of cell death may play important roles in neurodegenerative disorders, but this remains to be proven, and their relationship to inflammation has not been defined.

Innate Immune Mechanisms

Triggers of inflammatory reactions can engage the immune system at multiple levels. To begin with, they recruit the innate immune system. Subsequently, the acquired immune system may become involved also. The responses of resident CNS cells to injury are in many respects related more closely to the innate than to the acquired immune system. The innate immune system consists of phagocytes, natural killer cells, and molecules that mediate local inflammatory responses or support acquired immune responses (Figure 1). Components of the innate immune system in the CNS include microglia and astrocytes, which are strongly activated

in most neurodegenerative diseases and produce a variety of inflammatory mediators and other injury response factors (Eddleston and Mucke, 1993; Mennicken et al., 1999; Gasque et al., 2000; Akiyama et al., 2000; Nguyen et al., 2002).

Molecular Mediators

Innate immune responses are initiated by secreted molecules such as collectins or defense collagens (Tenner, 1999), which recognize diverse cellular and tissue abnormalities. Members of this group of proteins include surfactant protein A, calreticulin, and complement proteins such as C1q and mannose binding lectin. All have a collagen-like receptor binding domain and multiple globular domains that recognize pathogen-associated molecular patterns on microbes, dying cells, and abnormal protein deposits (Tenner, 1999). Binding of collectins to reactive surfaces can activate the complement cascade or mediate phagocytosis through the C1q receptor (Tenner, 1998). Besides the collectins, the complement protein C3 seems also able to specifically activate the complement cascade when bound to amyloid deposits, extracellular DNA, and dying cells (Sahu and Lambris, 2001; Fishelson et al., 2001).

Although the liver is the major source of complement, glial cells and neurons in the CNS can produce most of the 30 different proteins that make up the complex complement cascade. C1q, mannose binding lectin, and C3 stimulate the activation and chemotaxis of inflammatory cells, promote phagocytosis, and facilitate lysis by the membrane attack complex (Holers, 1996; Song et al., 2000). Levels of complement components are increased in AD (Gasque et al., 2000; Akiyama et al., 2000), PD (Yamada et al., 1992), and Huntington's disease (HD) (Singhrao, 1999). Complement activation products, including the membrane attack complex, colocalize with amyloid plaques and tangle-bearing neurons in AD (Webster et al., 1997b) and Down's syndrome (Stoltzner et al., 2000; Head et al., 2001). Using differential mRNA display, C1q B-chain mRNA was found to be strongly increased in an experimental model of prion disease (Dandoy-Dron et al., 1998).

What might be the consequences of complement activation in the degenerating CNS? Complement activation can lead to the formation of C3 convertases, multiprotein enzyme complexes that cleave the secreted complement factor C3 into C3a and C3b (Sahu and Lambris, 2001). C3a can promote chemotaxis of phagocytic cells. C3b binds covalently to acceptor molecules, initiating formation of the membrane attack complex and cell lysis. Alternatively, C3b deposition mediates phagocytosis through complement receptors on macrophages/microglia. Host cells are normally protected from spontaneous complement activation and self attack by a number of soluble or membrane-bound complement regulatory proteins (Holers, 1996). Whether complement activation in neurodegenerative disorders represents an appropriate injury response or results from an impairment of these regulatory systems remains to be determined.

In transgenic mouse models of immune-mediated CNS disease, inhibiting C3 complement activation decreased disease severity (Davoust et al., 1999). In contrast, eliminating C3 expression increased disease severity (Calida et al., 2001). Although the reason for this discrepancy is uncertain, there is additional evidence for a neuroprotective role of complement activation. For example, C3a and C5a bind to specific receptors on neurons (Nataf et al., 1999), and intraventricular infusion of C5a protected mice against glutamate-induced neurotoxicity (Osaka et al., 1999). This protection involved inhibition of caspase 3 by mitogen-activated protein kinase (Mukherjee and Pasinetti, 2001). Naturally C5-deficient mice were more susceptible to excitotoxic lesions than wild-type controls (Pasinetti et al., 1996). Perhaps even more surprising, sublytic concentrations of the membrane attack complex protected oligodendrocytes and Schwann cells from apoptosis (Fishelson et al., 2001). Finally, transgenic inhibition of C3 activation elicited a 2- to 3-fold increase in Aβ deposition and a prominent accumulation of degenerating neurons in hAPP transgenic mice (Wyss-Coray et al., 2002). These results suggest a role of complement activation products in protecting against Aβ-induced neurodegeneration and clearance of amyloid. They do not exclude the possibility that complement activation in neurodegenerative conditions may also have detrimental consequences of complement activation in neurodegenerative conditions (Pasinetti, 1998; McGeer and McGeer, 1999; Akiyama et al., 2000).

Effector Cells

Microglia and astrocytes, the main effector cells of innate immune responses in the CNS, are strongly activated in neurodegenerative diseases, producing an array of inflammatory mediators and fulfilling phagocytic functions (Eddleston and Mucke, 1993; Aldskogius et al., 1999; Benveniste et al., 2001). Microglia appear to be responsible for more generalized phagocytosis involving activation of the complement cascade, whereas astrocytes have been implicated in circumscribed phagocytic processes, such as the removal of individual synapses. Axotomy-induced synaptic degeneration in various experimental models results in rapid activation of microglia and astrocytes and subsequent elimination of damaged synapses (Kreutzberg, 1996; Aldskogius et al., 1999). The idea that imbalances between protective and destructive functions of microglia and astrocytes might contribute to neuronal or synaptic damage in neurodegenerative disease has appeal but remains to be proven experimentally.

Other effector cells of the innate immune system include nonclassical lymphocytes such as natural killer cells. These cells accumulate around degenerating nerve fibers and phagocytes in the axotomized facial motor nucleus (Raivich et al., 1998), demonstrating their ability to enter the brain and suggesting a potential role in neurodegeneration. Antigen-specific receptors on natural killer cells are less diverse than T cell receptors (TCRs), but some of them can interact with a limited number of MHC molecules (Bromley et al., 2001). Signaling of natural killer cell receptors is mediated by CD3ζ or by DAP-12 and other receptor-associated proteins with immunoreceptor tyrosine-based activation motifs in their cytoplasmic domain (Lanier and Bakker, 2000). Intriguingly, a loss-of-function mutation in DAP12 causes Nasu-Hakola disease, a presenile frontal dementia associated with axonal degeneration, widespread microgliosis, and microvascular degeneration (Paloneva et al., 2000). Thus, impaired function of natural killer cell recep-

tors or possibly of natural killer cells may lead to inflammation and degeneration of the CNS.

Probably the most efficient and aggressive phagocytes in the CNS are round or ameboid microglia, which express high levels of macrophage markers; in contrast, ramified (putatively resting) microglia have little phagocytic activity (Kreutzberg, 1996). Microglia associated with highly fibrillar amyloid plaques in AD brains show a ramified morphology even though they express activation markers (Dickson et al., 1993), suggesting that they might be nonphagocytic (DeWitt et al., 1998). However, upon activation in cell culture, microglia can ingest and degrade Aβ aggregates (Brazil et al., 2000; Wyss-Coray et al., 2001; Webster et al., 2001) or amyloid plaque cores from AD brains (DeWitt et al., 1998). Astrocytes may also participate in the phagocytosis of Aβ, either directly (Shaffer et al., 1995) (J. Huseman and T.W.-C., unpublished data) or by regulating microglial activities (DeWitt et al., 1998).

Amyloid fibrils have been detected in microglia of AD brains (Wegiel and Wisniewski, 1990; Frackowiak et al., 1992), and injection of fibrillar Aβ in rat brains resulted in a rapid accumulation of Aβ immunoreactivity in perivascular microglia (Frautschy et al., 1992). After vaccination of aged hAPP transgenic mice with Aβ, their amyloid burden was reduced, and Aβ colocalized with activated microglia in the brain (Schenk et al., 1999). Subsequent studies suggested that Aβ is cleared by microglia through Fc receptor-mediated phagocytosis (Bard et al., 2000). Consistent with these findings, activated microglia accumulated around Aβ deposits after topical administration of anti-Aβ antibodies in live mice (Bacskai et al., 2001). Increased microglial activation was also associated with reduced Aβ accumulation in hAPP transgenic mice overproducing the cytokine transforming growth factor β1 (TGF-β1) (Wyss-Coray et al., 2001) and in hAPP/presenilin 1 doubly transgenic mice treated with an antiinflammatory drug (Jantzen et al., 2002).

An alternative mechanism for the antibody-induced clearance of cerebral amyloid has recently been proposed (DeMattos et al., 2001, 2002). Infusion of anti-Aβ antibodies elicited a rapid rise in antibody-bound Aβ in the plasma. Based on this finding and ancillary evidence, the authors concluded that anti-Aβ antibodies might create a peripheral sink that augments a putative Aβ gradient between brain and blood "drawing" Aβ out of the brain parenchyma. Consistent with this notion, the extent of the antibody-induced surge in peripheral Aβ levels correlated with the cerebral amyloid burden (DeMattos et al., 2001, 2002). It is also conceivable that the infusion of certain anti-Aβ preparations increases the half-life of Aβ in the blood or induces a transient alteration of the blood-brain barrier, which could promote the leakage or transport of Aβ from the brain into the blood. These possibilities are not mutually exclusive and can be further tested experimentally.

Corpse Removal

Microglia and other phagocytes participate not only in the degradation of abnormal protein deposits and invading microbes, but also in the removal of degenerating host cells. Indeed, cell death and phagocytosis are often intricately linked (Giles et al., 2000; Savill and Fadok, 2000). In *Caenorhabditis elegans*, for example, cells that are programmed to die survive if genes involved in phagocytic engulfment are mutated (Reddien et al., 2001; Hoeppner et al., 2001). This finding suggests that phagocytes can deliver the lethal hit to cells undergoing apoptosis and that cells can retreat from this cell death program. In neurodegenerative diseases, potent survival factors may counteract proapoptotic signals (Hoeppner et al., 2001), giving phagocytic microglia the power to determine whether injured neurons live or die.

Much progress has been made in identifying factors involved in phagocytosis (Figure 2); they can be grouped into three broad categories. (1) Flags or "eat me" signals are expressed by dying cells, including phosphatidylserine, intracellular adhesion molecule-3, oxidized phospholipids, and altered carbohydrates (Giles et al., 2000; Savill and Fadok, 2000; Hengartner, 2001). (2) Recognition or tethering molecules, some of which may have signaling function, can be expressed at the surface of phagocytic cells. They include scavenger receptors, the vitronectin receptor, complement receptors, the phosphatidylserine receptor, the receptor tyrosine kinase Mer and related family members (Scott et al., 2001; Lu and Lemke, 2001), the lipopolysaccharide (LPS) receptor CD14 (Devitt et al., 1998), and calreticulin in combination with the low-density lipoprotein receptor-related protein (Ogden et al., 2001). Collectins and complement C3 are soluble recognition molecules that are secreted by phagocytic cells and can mediate interactions of dying cells with phagocytes (Mevorach et al., 1998). (3) Molecules involved in intracellular signaling in the phagocytic cell may participate in cytoskeletal reorganization and handling of ingested material. Genetic analysis in *C. elegans* has identified at least seven molecules in this category which appear to function in the removal of apoptotic or necrotic cells during larval development (Hengartner, 2001). Phagocytes in *C. elegans* can escalate programmed cell death by activating the caspase ced-3 (Reddien et al., 2001; Hoeppner et al., 2001), possibly to ensure that dying cells do not recover.

Intriguing evidence has been emerging that deficient phagocytosis might promote inflammation. Phagocytes engaged in the removal of apoptotic cells release antiinflammatory molecules, including interleukin-10, TGF-β1, lipoxins, and prostaglandin E2, and suppress the synthesis of proinflammatory factors such as tumor necrosis factor α (TNF-α) (Voll et al., 1997; Fadok et al., 1998, 2000; McDonald et al., 1999; Godson et al., 2000). Some of these antiinflammatory responses appear to depend on specific signals that emanate from apoptotic cells and are recognized by receptors on phagocytes. For example, the binding of apoptotic cells to CD14 on macrophages reduces TNF-α production, even though binding of this receptor by LPS or bacteria results in a proinflammatory response of the macrophage (Devitt et al., 1998). The antiinflammatory cytokine TGF-β1 is secreted directly from apoptotic cells, suppressing the release of inflammatory cytokines from macrophages in culture (Chen et al., 2001).

Studies of mutant mice lacking complement proteins suggest that deficient phagocytosis can indeed lead to immune-mediated tissue degeneration and inflammation in vivo (Botto et al., 1998; Taylor et al., 2000). Mice deficient in C1q developed glomerulonephritis associated with apoptotic bodies (Botto et al., 1998). Deficiency of C1q, and to a lesser extent of C4, also reduced

the clearance of apoptotic cells injected into the peritoneum (Taylor et al., 2000). Mice lacking the tyrosine kinase receptor Mer were blind and showed spontaneous accumulation of apoptotic cells in peripheral tissues, presumably due to a reduced ability of macrophages to phagocytose apoptotic cells (Scott et al., 2001). Mice lacking all three members of this kinase family (Mer, Axl, and Tyro3) were viable but showed increased apoptosis and accumulation of degenerating cells in peripheral tissues and in the hippocampus, cerebellum, and neocortex (Lu et al., 1999; Lu and Lemke, 2001). Notably, missense mutations in Mer cause retinal degeneration in rats (D'Cruz et al., 2000) and retinitis pigmentosa in humans (Gal et al., 2000), suggesting that defective phagocytosis can lead to inflammation and neurodegeneration in the CNS of both rodents and humans.

Acquired Immune Mechanisms

Although some inflammatory responses are present in insects and annelid worms, the core component of innate immunity, the complement system, first appeared in echinoderms (Zarkadis et al., 2001). Only vertebrates also developed acquired immunity, which is based on gene rearrangement of immune receptors (Finch and Marchalonis, 1996). Acquired immunity results in immunological memory through the production of immunoglobulins and lymphocytes (mainly T cells and B cells) carrying binding sites for specific antigens. That such immune responses could, in principle, contribute to neurodegenerative disorders is suggested by studies on other disease states. For example, in transgenic mice expressing the human CD4 receptor on microglia/macrophages, peripheral immune responses can trigger subacute neurodegeneration independent of CNS infiltration by immune cells, and this process may be relevant to some forms of HIV-associated dementia (Buttini et al., 1998). Antibodies directed against neuronal antigens may elicit neuronal dysfunction and neurodegeneration in stiff-person syndrome and various paraneoplastic syndromes, while both antibodies and cytotoxic T cells may be involved in the loss of neurons observed in Rasmussen's encephalitis (Whitney and McNamara, 1999; Archelos and Hartung, 2000; Bien et al., 2002).

The Expanding Role of MHC Molecules

Acquired cellular immunity has evolved to survey the body for abnormal proteins, either foreign or altered self. This remarkably complex task is carried out by T cells, which interrogate and recognize the proteinaceous content of cells at the so-called immunological synapse (Donnadieu et al., 2001; Bromley et al., 2001). Like the neuronal synapse, this structure supports the focal exchange of information between two cells across a specialized membrane structure. At the center of the immunological synapse are the MHC molecules and the T cell receptor. MHC class I molecules, together with β2-microglobulin, associate with peptides generated primarily from intracellular proteins by proteolytic degradation in the proteasome. At the cell surface, peptides are recognized in the context of MHC molecules by specific TCRs on T cells expressing the CD8 accessory molecule (Pamer and Cresswell, 1998). MHC class I molecules are present on all cell types and can be upmodulated by cytokines or neural injury. Neuronal populations affected by amyotrophic lateral sclerosis (ALS) or PD in humans increase their expression of MHC class I molecules in response to axotomy or interferon-γ stimulation in rats (Linda et al., 1998, 1999).

MHC class I expression on neurons is also regulated by electrical activity, and polymorphic variants of these molecules are expressed in unique subsets of neurons throughout the mature CNS (Neumann et al., 1997; Corriveau et al., 1998; Linda et al., 1998). Expression of MHC class I and β2-microglobulin mRNAs is markedly increased in tetrodotoxin-silenced neurons. CD3ζ, an adaptor molecule associated with the TCR and NK cell antigen receptors, was also increased in the silenced neurons. Subsequent studies in mice lacking functional MHC class I or CD3ζ demonstrated that both molecules are involved in CNS development and plasticity (Huh et al., 2000). The authors proposed that MHC class I acting at the neuronal synapse participates in activity-dependent elimination or refinement of synaptic connections and that the related signal transduction is mediated by CD3ζ and its associated kinase Fyn, which is important in neural plasticity (Kojima et al., 1997).

In neurodegenerative disorders, novel and potentially antigenic peptides may be derived from mutated or modified proteins or generated by abnormalities in the proteasomal pathway. Although such peptides could, in principle, be displayed to immune cells by neuronal MHC molecules (Figure 2), there is no convincing evidence in neurodegenerative disorders that neurons are a direct target for attack by cytotoxic T lymphocytes.

In contrast to MHC class I molecules, MHC class II molecules present peptides to immune cells that are derived primarily from extracellular antigens taken up into the endosomal/lysosomal pathway by phagocytosis, receptor-mediated endocytosis, or macropinocytosis (Watts, 1997). The resulting complexes engage specific TCRs on CD4-bearing T cells. Increased expression of MHC class II molecules is a classical marker of microglial cell activation. Microglial MHC class II expression is prominently increased in AD in association with amyloid plaques and degenerating neurons and in PD around degenerating dopaminergic neurons in the substantia nigra (McGeer et al., 1987; Akiyama et al., 2000).

Because MHC molecules appear not to be expressed at the cell surface in the absence of peptides (Watts, 1997; Pamer and Cresswell, 1998), increased MHC expression may reflect increased peptide presentation. But what peptides might be presented in neurodegenerative disease? Components of self proteins with abnormal conformations? Autoantigens released from damaged cells? Could interactions between microglia and T lymphocytes trigger pathogenic immune responses in the degenerating CNS? The answers to these questions are unknown.

Lymphocyte Invasion of the CNS

In patients with neurodegenerative diseases, T cells do not typically accumulate in significant numbers in the brain. However, there is evidence for more subtle T cell alterations. For example, T cell activation by Aβ and other APP-derived peptides is reduced in AD cases compared with nondemented controls (Trieb et al., 1996). T cells from hAPP transgenic mice also respond poorly to Aβ but normally to other antigens, indicating

the induction of relative T cell tolerance to Aβ (Monsonego et al., 2001). In contrast, blood levels of activated CD4-positive T cells were significantly higher in patients with PD and rats with PD-related neurodegeneration (Fiszer et al., 1994; Bas et al., 2001). Lymphocytic infiltrates and antibody deposits have been detected in postmortem CNS tissues from cases with familial or sporadic ALS (Troost et al., 1989; Kawamata et al., 1992). Proinflammatory changes in the CNS, including upregulation of intercellular adhesion molecule-1 and accumulation of immunoglobulins, preceded clinical disease manifestations in superoxide dismutase 1 transgenic mice, a model of ALS (Alexianu et al., 2001). Moreover, clonal expansion and activation of peripheral T cells was observed in patients with ALS or progressive muscular atrophy (Katchar et al., 2001), supporting the notion that autoreactive T cells may be involved in motor neuron disease.

The pathophysiological role and significance of these aberrant T cell reactions is not clear, since both CD4- and CD8-positive T cells can have detrimental or protective effects on the CNS. Cultured murine hippocampal neurons induced to express MHC class I molecules and pulsed with a viral peptide were rapidly damaged by virus-specific cytotoxic T cells (Medana et al., 2001). Damage was most prominent in neurites and included cytoskeletal breaks and the formation of neuritic spheroids, whereas the neuronal soma seemed to remain intact. In contrast, T cells recognizing self antigens may contribute to tissue repair after neuronal injury (Schwartz et al., 1999; Hohlfeld et al., 2000). When transferred into mice after optic nerve crush injury, activated myelin basic protein-specific T cells protected neurons from degeneration (Moalem et al., 1999). In the same model, induction of beneficial autoreactive T cells significantly enhanced the survival of retinal ganglion cells (Kipnis et al., 2001). Furthermore, genetic ablation of T and B lymphocytes in TNF-α transgenic mice worsened neurodegeneration and clinical signs (Stalder et al., 1998). Some of these findings may relate to the ability of autoreactive CD4- or CD8-positive T cells to secrete neurotrophins (Ehrhard et al., 1993). For example, myelin basic protein-specific T cells stimulated with antigen in vitro secreted brain-derived neurotrophic factor, and inflammatory CNS infiltrates in human cases with multiple sclerosis or disseminated autoimmune encephalomyelitis were immunoreactive for this factor (Kerschensteiner et al., 1999).

Autoantibodies—Culprits, Bystanders, or Protectors?

At least 50 reports in the literature describe antibodies against various CNS antigens in sera from AD patients. Autoantibodies against CNS antigens have also been reported in HD, Creutzfeldt-Jacob disease, ALS, and PD (Toh et al., 1985; Defazio et al., 1994; Leblhuber et al., 1998; Yi et al., 2000). Although the pathophysiological significance of these antibodies is unclear, they provide evidence of crosstalk between the degenerating CNS and the immune system. Many of these antibodies may originate in the periphery and enter the brain where the blood-brain barrier is leaky, but antibodies can also be produced locally by B cells that have entered the CNS or the subarachnoid space (Knopf et al., 1998). As outlined above, there are neurological diseases in which antibodies directed at neuronal antigens appear to play a causal role (Whitney and McNamara, 1999; Archelos and Hartung, 2000; Bien et al., 2002).

In line with the double-edged sword theme of this Review, antibody responses may also have beneficial effects in neurodegenerative diseases. For example, they can trigger or mediate the removal of potential neurotoxic protein aggregates. The vaccination-induced generation of antibodies against Aβ prevented and partially reversed AD-like pathological alterations and behavioral deficits in hAPP transgenic mice (Schenk et al., 1999; Janus et al., 2000; Morgan et al., 2000). The observation that AD patients have lower levels of anti-Aβ antibodies in the CSF than nondemented controls (Du et al., 2001) raises the possibilities of antibody sequestration by Aβ and of AD-related alterations in the response of B cells.

Names and Functions versus Roles of Inflammatory Mediators

Given the multiple functions of inflammatory factors, it is often difficult to determine their roles in specific pathophysiological situations. Cytokines and chemokines are key regulators of inflammatory processes and have been implicated in the pathogenesis of neurodegenerative diseases (Mennicken et al., 1999; Akiyama et al., 2000; Allan and Rothwell, 2001). They regulate the activity and survival of inflammatory cells and mediate the communication of immune cells with each other and with other cells of the body. Thus, the functions of these molecules in the immune system resemble those of neurotrophins and neuromodulators in the CNS. In fact, there is evidence for functional overlap between these groups of molecules. Neurons carry receptors for many cytokines and chemokines, suggesting an active crosstalk between the immune and nervous system. The chemokine fractalkine is expressed at higher levels in the CNS than in the periphery and has become known more recently as neurotactin (Mennicken et al., 1999). Many cytokines have neurotrophic effects and function in CNS development, and classical neurotrophins are also produced by lymphocytes (Ehrhard et al., 1993; Kerschensteiner et al., 1999).

Results obtained in genetically modified mouse models of CNS diseases suggest that altered expression of specific inflammatory factors may trigger or modulate the development of neurodegenerative disease. Neuronal apoptosis and cognitive deficits were identified in mice with neuronal overexpression of COX-2, an enzyme involved in the first steps of prostanoid synthesis (Andreasson et al., 2001) and the main target of the latest class of nonsteroidal antiinflammatory drugs (NSAIDs) (Zandi and Breitner, 2001). Astroglial overexpression of TNF-α, interferon-α, or interleukin-6 resulted in neurodegeneration, gliosis, and progressive neurological disease (Campbell et al., 1993; Akwa et al., 1998). The disease in TNF-α transgenic mice was even more pronounced when they lacked mature T or B lymphocytes, suggesting indirectly that microglia/macrophages are responsible for the pathogenic inflammatory process (Stalder et al., 1998). Surprisingly, mice lacking the receptor for TNF-α were more susceptible to ischemia and excitotoxic injury (Bruce et al., 1996; Sullivan et al., 1999), underlining how difficult it might be to predict the

outcome of therapeutic manipulations aimed at these molecules.

Even cytokines that likely fulfill primarily beneficial functions when expressed during acute phases of wound repair can have complex, including detrimental, effects if overexpressed for prolonged periods. For example, TGF-β1 is a major organizer of wound repair (Finch et al., 1993). However, TGF-β1 mRNA levels in postmortem AD brains correlated positively with the extent of cerebral amyloid angiopathy, and constitutive overexpression of TGF-β1 from astrocytes resulted in the deposition of Aβ in blood vessels in hAPP transgenic mice (Wyss-Coray et al., 1997, 2001). In contrast, overexpression of TGF-β1 diminished plaque formation in the brain parenchyma and reduced overall Aβ accumulation more than 50% (Wyss-Coray et al., 2001). This was associated with a prominent microgliosis, and in cell culture, TGF-β1 promoted microglial degradation of Aβ (Wyss-Coray et al., 2001). More recent studies showed that TGF-β1 overexpression increased the synthesis of C3 in hAPP transgenic mice and that inhibition of complement activation increased Aβ accumulation 2- to 3-fold. Complement inhibition in these mice was also associated with a prominent accumulation of degenerating neurons in the hippocampus (Wyss-Coray et al., 2002). These studies suggest that at least some components of the complement cascade fulfill neuroprotective roles in mice.

The findings reviewed above underline the importance of differentiating between the function(s) a molecule can fulfill and the specific role it plays in a particular disease. The latter may depend critically on where, when, for how long, and in what context the molecule is produced. Because of the multifunctionality of many inflammatory molecules, their altered CNS expression does not necessarily imply the presence of an inflammatory or immune-mediated process in the CNS. This differentiation has implications for the design of better treatments for neurodegenerative disorders.

To Suppress or to Direct the Inflammatory Machinery

The ultimate proof that a suspected process contributes critically to a disease would ideally come from human trials in which the pathogenic process is blocked effectively and specifically. Unfortunately, it is not always easy to assess how effectively a suspected pathogenic process was blocked in individual patients, and many compounds have numerous actions besides those for which they are prescribed. For example, tetracyclines, which are frequently used to treat infections in humans (and to regulate transgene expression in mice), have not only antimicrobial but also antiinflammatory and antioxidant activities (Yrjänheikki et al., 1999; Chen et al., 2000; Tikka et al., 2001). Even more pertinent to this review is the recent finding that certain NSAIDs inhibit the production of Aβ (Figure 3) independently of COX, the main pharmacological target of these drugs (Weggen et al., 2001). This observation is particularly intriguing in light of the many epidemiological studies demonstrating an association between the use of NSAIDs and reduced AD risk (McGeer et al., 1996; Zandi and Breitner, 2001).

In line with these reports, treatment of hAPP transgenic mice with the NSAID ibuprofen reduced Aβ accumulation, proinflammatory cytokine production, and microglial activation around plaques (Lim et al., 2000). Similarly, treatment with NO-flurbiprofen, a nitric oxide-donating NSAID, celcoxib, a COX-2 antagonist, or ibuprofen also resulted in reduced Aβ deposition in hAPP/presenilin-1 doubly transgenic mice (Jantzen et al., 2002). NO-flurbiprofen, which had the strongest inhibitory effect on Aβ accumulation, resulted in a striking activation of microglia in hAPP/presenilin-1 transgenic mice but not in nontransgenic controls (Jantzen et al., 2002). NO-flurbiprofen also increased microgliosis in aged rats that had been chronically infused with LPS but not in similarly treated young rats (Hauss-Wegrzyniak et al., 1999), indicating that microglia may respond differently to NSAIDs depending on age and the presence of other inflammatory triggers in the brain.

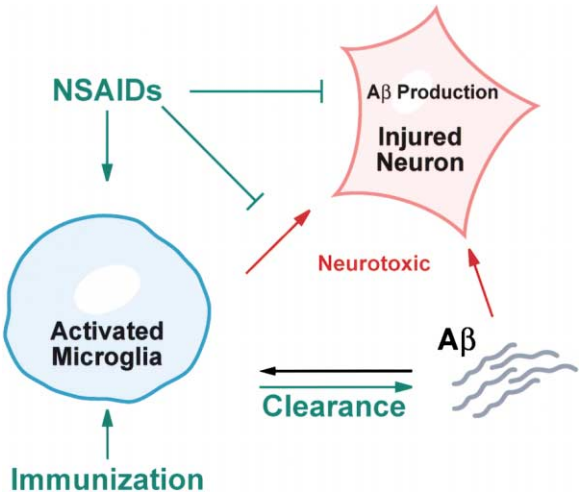

Figure 3. Turning the Right Side of the Inflammatory Sword against AD

Neurotoxic assemblies of Aβ peptides (gray wavy lines) presumably injure neurons and activate glia in AD brains. While some glial products can be neurotoxic, other glial products and activities protect neurons and help remove Aβ aggregates. Treatment with NSAIDs or vaccination with Aβ appears to tip the balance from detrimental to beneficial glial activities and inhibits the accumulation of Aβ in the brain. NSAIDs, nonsteroidal antiinflammatory drugs. Detrimental effects are depicted in red, beneficial effects in green.

The link between NSAID use and reduced AD risk has been interpreted as evidence for a causal link between brain inflammation and AD (McGeer et al., 1996; Stewart et al., 1997; Pasinetti, 1998). The recent findings by Weggen et al., 2001, raise the possibility that the observed association is due, at least in part, to a reduction in Aβ levels. Ongoing trials should reveal whether NSAIDs with Aβ-reducing capacity can prevent or stall the development of AD. No significant effects were observed on the progression of AD in treatment trials with a variety of compounds that strongly suppress inflammation, including corticosteroids (Aisen, 2000), diclofenac/misoprostol (Scharf et al., 1999), COX-2 inhibitors (Zandi and Breitner, 2001), and hydroxychloroquine (Van Gool et al., 2001).

Thus, it remains uncertain to what extent inhibiting inflammation can reduce neurodegenerative disease. In

fact, several recent findings suggest that specific inflammatory responses may be beneficial. For example, inhibiting the activation of C3 complement component increased, rather than decreased, Aβ deposition and neurodegeneration in hAPP transgenic mice (Wyss-Coray et al., 2002). Eliciting a vigorous antibody response to Aβ in hAPP transgenic mice prevented and partially reversed AD-like pathology and behavioral deficits (Schenk et al., 1999; Janus et al., 2000; Morgan et al., 2000). These findings propelled this therapeutic strategy into the clinic, where it recently met with obstacles that highlight the double-edged sword of inflammation (Senior, 2002). In a phase I trial, 64 patients received six to eight doses of the Aβ vaccine, and no significant immunological side effects were observed. However, in a subsequent phase II trial, in which 300 patients received one to three doses of the vaccine (in a slightly different formulation), 15 developed signs and symptoms consistent with meningoencephalitis. None of 75 additional placebo control cases developed such side effects. It is likely that the vaccine-induced complications relate to the immunologic diversity of the immunized AD population.

The presence of autoantibodies against Aβ and the decreased responsiveness of T cells to Aβ in some but not all AD patients provides evidence for diverse immune responses against this peptide (Trieb et al., 1996; Hyman et al., 2001; Myagkova et al., 2001). Because specific immune recognition requires the association of the immunogenic peptide with polymorphic MHC molecules, individuals with certain MHC molecules may be more prone to mounting a detrimental rather than a beneficial immune response to Aβ. Ongoing studies focus on determining how the immune system and its responses differ in patients that did or did not tolerate the vaccination. Based on these and related studies, it may be possible to prescreen and exclude at-risk patients from future trials. Alternate approaches that might be explored include intranasal vaccination (Weiner et al., 2000), vaccination with Aβ oligomers (Klein et al., 2001) or immunoconjugates designed to elicit primarily B cell responses and microglial activation, and infusion of anti-Aβ antibodies that induce microglial clearance of Aβ aggregates in the brain (Bard et al., 2000; Bacskai et al., 2001) or sequester Aβ in the circulation (DeMattos et al., 2001, 2002).

The studies reviewed above suggest that the outcome of inflammatory responses depends on the specific trigger and on the genetic background on which it occurs. It has previously been shown that the molecular profile of activated microglia differs depending on the type of neural injury to which they respond (Flaris et al., 1993). Inheritance of the MHC class II molecule HLA-DQ7 protected humans against variant Creutzfeldt-Jacob disease, a condition caused by a bovine spongiform encephalopathy-related prion strain. Conceivably, presentation of abnormal prion proteins to immune cells by HLA-DQ7 molecules might elicit immune-mediated protection against the disease (Jackson et al., 2001). Presentation of abnormal peptides by neuronal MHC molecules might also affect their putative functions in neuronal plasticity (Boulanger et al., 2001). Other genetic determinants that could influence the outcome of inflammatory responses include polymorphisms in genes encoding cytokines or other injury response factors (Mahley and Huang, 1999; McGeer and McGeer, 2001).

Conclusions

Neurodegenerative disorders are associated with a variety of inflammatory responses whose precise roles in these conditions remain to be defined. Much more needs to be learned in general about the functions of inflammatory and immune molecules in the normal and diseased CNS. A better understanding of specific molecular pathways in activated glial cells may help reconcile apparently contradictory outcomes of inflammatory responses. Since many of these responses can exert potent beneficial effects, directing and instructing the inflammatory machinery may be a better therapeutic objective than suppressing it. It is interesting to note in this context that the immune system and the CNS are shaped by both genetic and environmental determinants. Therefore, optimizing immune modulatory treatments for neurological diseases may require detailed information not only on the genome but also on the proteome of individual patients.

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