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Viral and Inflammatory Triggers of Neurodegenerative Diseases

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Abstract

Here, we synthesize research behind the emerging hypothesis that inflammation—which can result, for example, from viral infections—can initiate and propagate chronic neuronal dysfunction, an event that precedes the clinical onset of many neurodegenerative diseases. Therapeutic approaches that target immunological pathways in the prodromal phase of diseases might decrease the incidence of neurodegenerative disorders and increase the therapeutic window for neuroprotection.

The relationship between viral infections and neurodegeneration remains largely unknown. In this Perspective, we discuss an intriguing hypothesis: that viral infections and inflammation prime neurons and immune cells in the brain, rendering neuronal populations vulnerable to degeneration in the face of subsequent insults. These activated inflammatory pathways may represent opportunities for therapeutic intervention before the onset of neurodegenerative disease.

DISEASE NEXUS

Viruses defined as neurotropic preferentially infect neurons and can cause severe, and sometimes fatal, brain inflammation (encephalitis). More commonly, viruses enter the central nervous system (CNS; the brain and spinal cord) asymptomatically during systemic infections either by crossing the blood-brain barrier (BBB) or via the peripheral nervous system (PNS; nerve tissue outside of the CNS) (1). There is correlative evidence that the infection of neurons and neighboring glial cells and the accompanying increase in cytokine proinflammatory mediators can trigger cell dysfunction and increase neuronal vulnerability to other neurodegenerative insults, such as those caused by aging, oxidative stress, environmental toxins, or genetic predisposition. The influenza pandemic that occurred toward the end of World War I was associated with a dramatic increase in postencephalitic parkinsonism (PEP) (also called sleeping sickness or von Economo encephalitis) in the 1920s and 1930s (2).

Moreover, human populations infected with Japanese encephalitis virus (JEV) for longer than one year are likely to develop PEP, which is characterized by many of the same neuropathological and locomotor symptoms as those seen in patients with sporadic

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Parkinson's disease (PD) (3). More recently, experimental inoculation of mice with the influenza virus H5N1 was shown to simulate many aspects of PD-like initiation and pathogenesis. The systemic infection progressed with virus entry in the PNS, followed by brain entry. The ensuing and lasting inflammation in the track of the virus resulted in the dysfunction or degeneration of vulnerable dopamine (DA)–producing neurons in midbrain regions, as is seen in PD patients (4, 5).

INFLAMMATION ON THE BRAIN

Although a wide variety of data indicate that inflammation is involved in the progression of neurodegenerative diseases, less is known about inflammation's role in disease onset and neuronal susceptibility to degeneration. One emerging hypothesis is that neuroinflammation plays a critical role in priming vulnerable neuronal populations for subsequent degeneration. Several lines of evidence support a role for inflammation in disease pathogenesis, including the initiation of neuronal dysfunction. These include the increased concentrations of proinflammatory cytokines that are seen in the early stages of neurodegenerative diseases (6) and the association of these diseases with certain genetic variants in the region of chromosome 6 that specifies the human leukocyte antigens (HLAs) (7), which are crucial for immune function in humans.

The potential role of the immune system in the initiation of neuronal degeneration has been documented in Huntington's disease (HD) and acquired immunodeficiency syndrome dementia complex (8–10). Peripheral immune activation occurs before disease onset in HD and correlates with an increase in proinflammatory cytokines, such as interleukin-6 (IL-6) and IL-8, in cerebrospinal fluid (8). Furthermore, activation of microglia—brain macrophages within brain areas associated with cognitive dysfunction—predict HD onset (8). Immune activation has been documented in the early phases of Alzheimer's disease (AD) in patients (6). Proinflammatory cytokines such as tumor necrosis factor–α, IL-1β, and interferon-γ (IFNγ) stimulate the production of β–amyloid precursor protein and its processing of amyloid β peptides, which accumulate in AD (11, 12).

Several recent studies in rodent models of PD demonstrate that neuroinflammation can precipitate PD-like pathology (13–19). Recent data also show that loss of midbrain DA-producing cells (a hallmark of PD) and striatal degeneration can be preceded by neuroinflammation marked by activated microglia and an increase in proinflammatory cytokine concentrations (18). Such neuroinflammatory responses activate a cascade of events that corresponds to changes observed in early neurodegeneration (16, 18).

We suggest that neurodegeneration can be triggered and then propagated by repeated inflammatory reactions (such as local production of cytokines) over time. Indeed, there is evidence for both microglial and astrocytic (star-shaped glial cells in the brain) activation and reactions that track existing neuronal circuits in the CNS and PNS (4, 16, 18, 19). These inflammatory sequences combined with regional and cell type–dependent neuronal vulnerability could cause the specific structural and functional neurodegenerative patterns that define individual neurodegenerative diseases (Fig. 1A).

BRAIN IMMUNE RESPONSES TO VIRAL ATTACKS

Viruses can induce brain dysfunction by either direct cytolytic effects or bystander inflammatory reactions (20). Neurotropic viruses (for example, arboviruses, influenza viruses, herpes viruses, polyomaviruses, and rotaviruses) have developed mechanisms to escape host immune surveillance and gain access to the CNS. Primary infection of neurons then trigger acute cell dysfunction, which can result in lethal encephalomyelitis (21). The lack of appropriate immune strategies for viral eradication may also result in long-lasting

subclinical infections. The systemic and local inflammatory responses to viruses are potential key contributors to neuronal damage, even in the absence of overt cell death. Viruses elicit CNS inflammation either by entering the brain through a damaged BBB or along the peripheral nerves or by activating the innate and adaptive host immune system in the periphery (Fig. 1B) (20, 21).

The innate immune response is an early line of defense against microbes (bacteria or viruses) that is launched in the first hours of infection. Viral proteins and nucleic acids are recognized by a family of evolutionarily conserved cell-surface host proteins, the toll-like receptors (TLRs). Specifically, TLR3 detects double-stranded RNA (dsRNA), whereas TLR7 and TLR9 recognize single-stranded RNA (ssRNA) and ssDNA. TLRs are highly expressed on antigen-presenting cells such as B lymphocytes, dendritic cells, monocytes, macrophages, and microglia. In addition, these receptors can be expressed by the cerebral endothelium, astrocytes, myelin-producing oligodendrocytes, and neurons (22). Activation of TLRs triggers the production of antiviral mediators, such as type I IFNs and proinflammatory cytokines and chemokines. Importantly, this peripheral cytokine storm is accompanied by increased amounts of proinflammatory mediators in the CNS (Fig. 1B) (23, 24).

NEURONS AND GLIA AS IMMUNE SENSORS

Historically, glial cells have been thought to be the main contributors to cytokine and chemokine production and the presence of immune receptors in the brain. However, there is increasing evidence that neurons also express molecules originally thought to be specific to the immune system (25). These immune receptors are known to function in the development and organization of neuronal networks and synapses. These multifunctional molecules may also carry out their classical functions—modulating the innate immune response in the brain; indeed, neurons appear to be capable of sensing and responding to viral infections (26).

Support for this hypothesis comes from several observations. First, researchers have shown in rodents that neurons can initiate and perpetuate innate immune responses in the brain even in the absence of traditional immune cells (astrocytes, oligodendrocytes, and microglia) (Fig. 1B) (27–29). Second, TLR3 and TLR8 are expressed on mouse and rat neurons that inhibit neurite outgrowth in response to viral mimics such as dsRNA. Such autonomous activation of brain innate receptors during viral infections could, therefore, contribute to reduced repair of brain connections and the subsequent neuronal dysfunction. Third, in humans, TLR3 is up-regulated on neurons in viral CNS infections such as Herpes simplex encephalitis (30), and overexpression of neuronal TLR3 has also been reported in the context of stroke and neurodegenerative diseases, such as amyotrophic lateral sclerosis and AD, although whether this enhanced expression contributes to disease pathogenesis remains unclear (30).

Notably, injection of a compound that mimics virus dsDNA into rodent brain induces a prominent up-regulation of inflammatory cytokines and a long-lasting inflammatory reaction (16). Specifically, this virally induced inflammatory environment triggers neuronal changes observed in early neurodegeneration, including altered concentrations of proteins relevant to axonal transport and synaptic transmission (16, 18). Synapses and axons are early targets of inflammation-induced neurodegeneration, and many data support the hypothesis that neurodegenerative changes are preceded by synaptic and axonal pathology in vivo (31). Clearly, in disease-model conditions such as experimental autoimmune encephalomyelitis in mice—a model for multiple sclerosis—inflammation promotes synaptic degeneration and loss of dendritic spines, which are the receptive branch protrusions of neurons (32). Synaptic

dysfunction also occurs prominently in the early stages of AD pathogenesis and is one of the best pathological correlates of cognitive decline in human patients (33); clinically, systemic inflammation and the subsequent increase in peripheral proinflammatory cytokines are associated with a marked cognitive decline in these patients (34). In the brain, IL-1β may have a direct role in age and oxidative stress–induced impairments of neuronal function and subsequent degeneration (35). Synaptic failure has also been detected in the early stages of experimental DA-neuron pathology in animal models of PD (36). In these rodent models, increased amounts of α-synuclein impair the release of the neurotransmitters glutamate and dopamine, which in turns leads to a broad synaptic dysfunction (36). Accumulation of the α-synuclein protein in neural cells is a hallmark of PD. Taken together, these data highlight the potential involvement of inflammatory pathways in early synaptic loss and axonal dysfunction.

There are well-documented but rare recent instances in which acute severe encephalitic viral disease was shown to directly cause transient symptomatic PD with evidence of DA neuron–midbrain structural involvement (37) or permanent clinical neurological symptoms, including parkinsonism (38–40). However, the central premise of the hypothesis presented here is not that a linear relationship exists between the viral infection, brain inflammation, and an acute manifestation of neurodegenerative disease. Indeed, neither viral presence nor peak load correlate with the time when neurologically important, irreversible neurodegeneration has occurred (4, 41). Instead, we suggest that a causal relationship exists between viral infection–associated inflammation and cytokine-induced sequela that together prime relatively specific groups of vulnerable neurons to degenerate, in response to other cellular insults (42), at higher rates than those observed during normal brain aging (13, 16). Hence, our prediction is that frequent, sustained, or particularly severe periods of neurologically “silent” (nonsymptomatic) brain inflammation predispose individuals to develop common sporadic forms of several well-described neurodegenerative diseases later in life.

GENETIC VULNERABILITY

Genetic susceptibility to neurodegeneration can accelerate neuron loss in response to triggers of inflammation. In this context, overexpression of wild-type and pathological forms of human α-synuclein or production of nonfunctional versions of the Parkin protein, which causes a familial form of PD, increases the vulnerability of midbrain DA neurons to inflammation-induced degeneration (14, 15).

Although there is no evidence that neurodegenerative diseases are caused directly by viruses, aberrant inflammatory reactions triggered by viral infections could initiate neurodegeneration, preferentially in individuals who are at risk for neurodegenerative disorders as a result of individual genetic mutations or epigenetic differences that modulate the immune response or susceptibility to infectious diseases (43, 44). For example, a polymorphism in the gene that encodes the major histocompatibility complex class II cell surface receptor HLA-DR was shown recently to be a risk factor for PD 6. Also, a high risk for AD has been shown to manifest when Herpes simplex virus type 1 infects individuals who carry the *ApoE4* genotype, which is involved in viral clearance (45).

Last, interactions between genetic and environmental factors probably also determine a person’s immune responsiveness to pathogens, which in turn influences susceptibility to neurodegeneration. A very recent report has shown that mice that lack the gene that encodes the cell signaling protein leucine-rich repeat kinase 2 (LRRK2)—which, when mutated, is the most common genetic cause of PD in humans—display hyperactive immune responses and increased susceptibility to inflammatory bowel disease by regulating the transcriptional

regulatory protein nuclear factor of activated T cells relative to control mice (46). Expression of the *LRRK2* gene is regulated by IFN-γ and is potentially involved in immune responses to pathogens (47, 48). In individuals who carry mutations in the *LRRK2* or the α-synuclein–encoding *SNCA* genes, common viral infections, such as those caused by gastrointestinal pathogens, may initiate aberrant inflammatory responses and subsequent dysfunction of the autonomic nervous system (for example, in the digestive or cardiovascular systems, conditions that are associated with the prodromal phase of PD) (49–51).

TRANSLATIONAL HORIZONS

On the basis of the data and ideas presented here, we propose that untreated preconditions that set the stage for the development of common neurodegenerative diseases may be targets for neuroprotective therapeutic strategies. A detailed understanding of the molecular mechanisms at work in virally and other–induced neuroinflammation is crucial if researchers are to uncover ways to regulate aberrant cytokine–induced initiation and propagation of neuronal damage. Precise predictive models of the prodromal phase of neurodegeneration will provide guidance for the pinpointing of therapeutic targets and designing of intervention regimens that delay disease onset and, thus, reduce the human suffering and impact of neurodegenerative disease.

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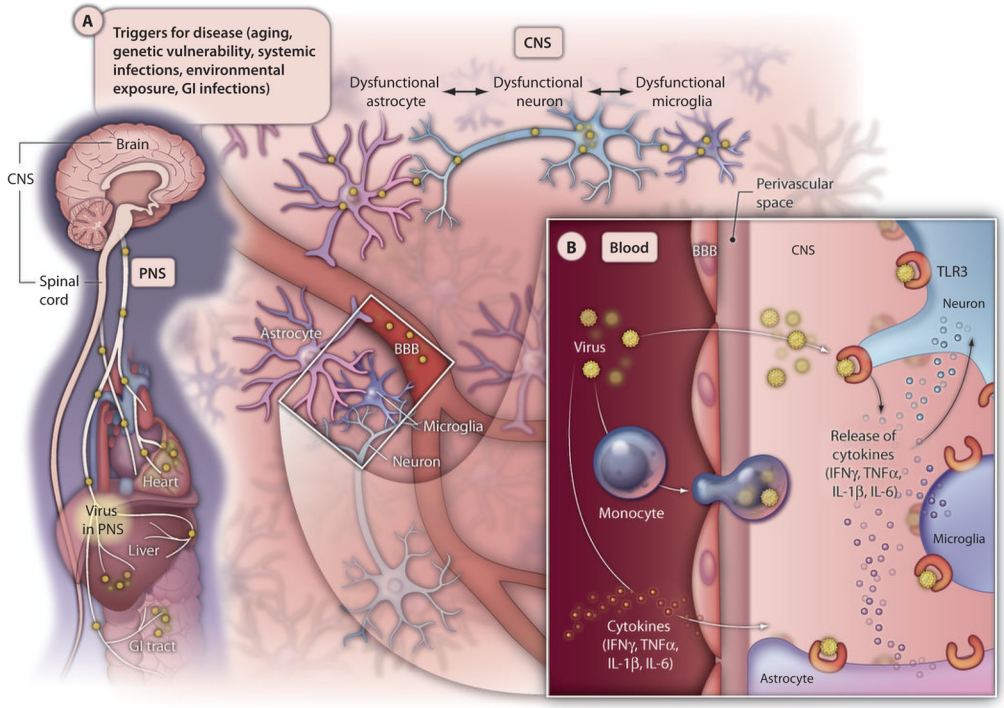

Fig. 1. Driving dysfunction

(A) Triggers of neurodegeneration. Idiopathic neurodegenerative diseases result from the combined action of multiple risk factors that include genetic predisposition, age, and environmental triggers, such as toxins and inflammatory responses involving microglia and astrocytes. In one such scenario, common viral infections can trigger peripheral local inflammatory responses, which lead to early neuronal and glial dysfunction in the CNS. Peripheral inflammatory reactions can also initiate neurodegenerative changes in the PNS, which are often associated with the preclinical phase of many neurodegenerative diseases. Such induced acute or chronic inflammation, involving cytokines and activated glial cells, could therefore be responsible for the priming of the PNS and CNS to degeneration by reducing the threshold for irreversible neuronal damage resulting from any subsequent neurotoxic trigger. Genetic susceptibility to neurodegeneration can also accelerate neuronal damage in response to inflammatory triggers. **(B)** Viral invasion and inflammation. Viruses can trigger neuronal dysfunction by direct cytolytic effect, direct neuronal priming, or bystander inflammatory reactions. Neurotropic viruses can reach the CNS by crossing the BBB or via peripheral nerves. The infection of neurons induces acute cell death, which is accompanied by secondary inflammatory reactions. Such neurotropic viruses often induce fatal encephalomyelitis. Nonneurotropic viruses can also invade the brain and trigger local CNS inflammation. Neurons sense and respond to viruses through the expression of TLRs (shown here as TLR3), which leads to the activation of an intracellular signaling cascade culminating in cytokine and chemokine secretion. The activation of neuronal TLRs by viral challenges and the primary inflammatory reactions may exert a priming action directly on neurons, rendering them more vulnerable to neurodegeneration.. GI tract, gastrointestinal tract.