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REVIEW

How neuroinflammation contributes to neurodegeneration

Richard M. Ransohoff

Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and frontotemporal lobar dementia are among the most pressing problems of developed societies with aging populations. Neurons carry out essential functions such as signal transmission and network integration in the central nervous system and are the main targets of neurodegenerative disease. In this Review, I address how the neuron's environment also contributes to neurodegeneration. Maintaining an optimal milieu for neuronal function rests with supportive cells termed glia and the blood-brain barrier. Accumulating evidence suggests that neurodegeneration occurs in part because the environment is affected during disease in a cascade of processes collectively termed neuroinflammation. These observations indicate that therapies targeting glial cells might provide benefit for those afflicted by neurodegenerative disorders.

The human central nervous system (CNS) might represent the most complex entity in existence, although conclusive evidence to support or falsify that hypothesis will probably forever be elusive. Nonetheless, the CNS is beyond question the most elaborate system of which we have daily experience. CNS disorders alter and often degrade the structure and function of this intricate organ. Neurodegeneration is a common (but not invariable) component of CNS disorders and includes processes by which previously established CNS functions such as mobility, memory and learning, judgment, and coordination are progressively lost. Neurodegenerative diseases primarily occur in the later stages of life, positioning time as an essential cofactor in pathogenesis of the major neurodegenerative disorders in a mechanism-driven fashion (*1*–*3*). The achievements of medicine and public health efforts in reducing early- and midlife mortality from certain cancers, infectious diseases, and cardiovascular disorders mean that a larger number of individuals are aging and therefore susceptible to neurodegenerative disease by virtue of their survival. The large cohort of aging people in the developed world threatens society with a substantial burden of care for those afflicted with neurodegeneration (*4*). Moreover and most poignantly, these diseases rob affected persons of those attributes that make long lives worth living: thinking, feeling, remembering, deciding, and moving. Here I consider neuroinflammation in neurodegeneration, a topic that comprises most of the nonneuronal contributors to the cause and progression of neurodegenerative disease. The study of this topic is animated by our hope that meaningful action, in the form of novel treatments, will follow understanding.

What is neurodegeneration?

Neurons are the primary cells of the CNS and endow it with its distinctive functions. Connections between neurons are enacted at synapses, where neurotransmitters are released in quanta to deliver an excitatory or inhibitory signal to the synaptic-target neuron. Cell processes that deliver these signals are termed axons, whereas dendrites receive synaptic inputs. Each of the ~10^{11} neurons in the human brain integrates many synaptic inputs from other neurons and, for each input received, may or may not initiate an axonal action potential and thereby provide synaptic input to its target neuron—a system comprising 10^{15} connections in all.

> ***"Neuroinflammation has been famously difficult to define in relation to neurodegenerative disease."***

Neurodegeneration by definition disturbs the properties of the CNS and therefore affects neuronal function, as well as the structure or survival of neurons. Unlike primary cells from skin, the liver, or muscle, neuronal cells of the CNS do not regenerate after damage by disease, ischemia (deprivation of oxygen, glucose, or blood flow), or physical trauma. Because the complexity of the human CNS is so great, neurodegenerative disorders that derange its function have been challenging to understand and treat: No therapeutics ameliorate the natural course of neurodegenerative disease.

Major neurodegenerative diseases include Alzheimer's disease (AD), frontotemporal lobar dementia (FTLD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Individuals diagnosed with multiple sclerosis (MS) are also at risk of developing a neurodegenerative course, typically at later stages of the disease; such cases are termed progressive MS (P-MS). One might consider that AD, PD, and ALS are primary neurodegenerative diseases, in which the initial

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Table 1. Protein aggregates in neurodegenerative diseases. A-β, N-terminal amyloidogenic fragments of APP; MAPT, microtubule-associated protein tau; TDP-43, 43-kDa TAR DNA-binding protein.

Composition of aggregate	Associated disorders	Physiological localization	Localization in disease
A-β	AD, PDD	Membrane	Extracellular
MAPT	AD, FTLD-tau	Axonal	Cytoplasmic
α-synuclein	PD, PDD	Synaptic	Cytoplasmic
TDP-43	ALS, FTLD-TDP	Nuclear	Cytoplasmic

signs of pathology affect neurons. By comparison, neurodegeneration in P-MS appears to be secondary to the initiating events, which target CNS myelin.

Those studying neurodegenerative conditions rely on a shared set of research tools. Among many others, neurodegeneration researchers draw from neuropathology (analysis of affected tissue), genetics, and model systems. Most neurodegenerative disorders directly affect only the nervous system and specifically the CNS (brain, spinal cord, and optic nerve), as distinguished from the peripheral nervous system (PNS), which encompasses the nerves and muscles of the body and its internal organs. Over many decades of dedicated study, neuropathologists have found that discrete populations of neurons are lost or impaired in each of these diseases—for example, pigmented dopamine neurons in PD and neurons of the motor system in ALS. Additionally, AD, ALS, FTLD, and PD feature characteristic protein aggregates within neurons; representative instances are neurofibrillary tangles in AD and Lewy bodies in PD. A distinctive tissue change termed amyloidosis, in which extracellular proteins are arrayed in beta-pleated sheets, typifies the cortex and hippocampus in AD and in PD with dementia (PDD) (Table 1). In both AD and PDD, N-terminal fragments of amyloid precursor protein (APP) are the major constituents of the extracellular amyloid deposits. Discovering the neurons targeted by each disease and identifying disease-selective pathological protein aggregates has enabled substantial progress in understanding these disorders.

A small minority (<5%) of patients affected by AD, PD, ALS, or FTLD demonstrate Mendelian inheritance of their disease. Furthermore, for each disorder and each major constituent of the characteristic protein aggregate, rare mutations of the encoding genes validate a causal relation between mutant proteins and disease (*5*–*7*). For the most part, disease manifestations of the Mendelian forms of neurodegeneration phenocopy those of the sporadic cases, save only for earlier onset in the case of the former. For this reason, it is considered highly likely that a pathogenic relationship also holds between protein aggregates and disease for sporadic cases. Given their importance for categorizing distinct disorders, the protein aggregates are used in a new molecular nosology that includes synucleinopathies, tauopathies, and amyloidoses. Researchers have accumulated substantial evidence favoring the interlinked hypotheses that relate protein aggregates to sporadic neurodegenerative disease. Nonetheless, only successful therapeutic trials targeting protein aggregates, their upstream causes, or their downstream effects will confirm that these devastating diseases are indeed caused by processes related to protein aggregates.

The current paradigm for these major primary neurodegenerative diseases includes additional commonalities. First, neurodegenerative diseases including PD, AD, and FTLD demonstrate a predictable temporospatial pathological evolution, involving one brain region followed by another and then another. It has been proposed that this mode of progression is mediated at least in part by the transfer of pathogenic protein forms between adjacent cells (*8*, *9*). It is important, however, to emphasize that this intra-individual spreading of pathogenic protein, although reminiscent of prion disease, is not proposed to be associated with risk of exposure to affected persons or their tissues (*10*). Furthermore, although cell-to-cell spread of fibrillar forms of pathogenic proteins can be demonstrated experimentally, its

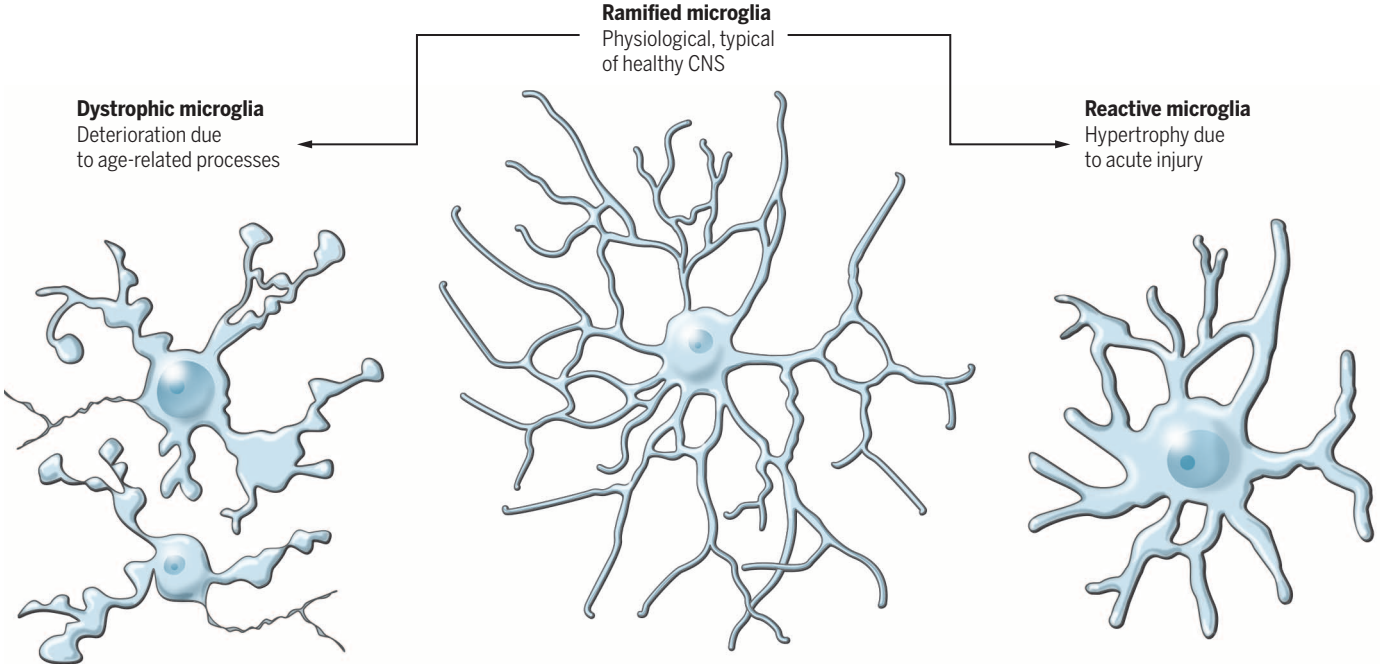

Fig. 1. Morphology of ramified (healthy CNS), reactive, and dystrophic microglia. Microglia reflect their response to the environment in part through their morphology. Morphology does not reliably reflect function, dysfunction, or RNA expression profile phenotype but only demonstrates that the cell is responding to altered homeostasis (*76*). The cartoon depicts three states of microglial morphology: ramified (physiological) microglia, typical of those observed in the healthy CNS; reactive microglia, characteristic of those seen after acute injury; and dystrophic microglia, as observed in the aging brain, particularly in the context of neurodegeneration.

Table 2. Selected elements of the CNS neuroinflammatory system.

Name	Category	Peripheral counterpart	Peripheral function	CNS function
Microglia	Myeloid cell	Circulating monocyte or tissue macrophage	Host defense, wound repair	Synapse formation (*58*), refinement (*59*), monitoring (*60*), and maintenance; inflammatory response; adult neurogenesis modulation (*61*, *62*)
Astrocyte	Glial cell	None	Not applicable	Glutamate reuptake, ionic buffering, water balance, energy substrate for neurons, BBB maintenance (*63*), inflammatory response (*64*, *65*)
Oligodendrocyte	Glial cell	Schwann cell	Myelination of peripheral axons	Myelination of CNS axons, trophic support for myelinated axons (*66*)
$NG2^+$ glia	Glial cell	None	Not applicable	Precursor to adult oligodendroglia (*67*, *68*), inflammatory response (*69*)
CX3CR1	Chemokine receptor	Same as CNS	Monocytes patrolling vessel walls, inflammatory response	Neuron-glia interactions (*50*, *70*, *71*)
C1q, C3, C4, CR3	Complement components	Same as CNS	Host defense	Synaptic pruning (*72*)
TNF-α	Cytokine	Same as CNS	Host defense, inflammation	Synaptic scaling (*73*), neuroprotection (*74*, *75*)

role in disease progression is not a matter of universal agreement. It remains plausible instead that pathology occurs serially in vulnerable neuronal populations, which are proposed to have increasing regionally restricted frequency in the aging brain (*11*). Second, it is hypothesized that protein aggregates, although visually striking when viewed in tissue sections, may not in all cases represent the crucial pathogenic alteration, but rather that their fibrillar or oligomeric precursors may have direct neurotoxicity (*11*). Third, it is widely held that defects in mitochondrial function and turnover (termed mitophagy), autophagy, and management of oxidative stress are involved in various ways in each of these disorders (*12*).

What is neuroinflammation?

Neuroinflammation has been famously difficult to define in relation to neurodegenerative disease. In contrast, neuroinflammation in multiple sclerosis (MS) is unambiguous, comprising often florid infiltration of the CNS parenchyma by blood-derived lymphocytes and monocyte-derived macrophages, accompanied by frank impairment of blood-brain barrier (BBB) function and intense glial reaction. Neuroinflammation in diseases such as AD, PD, and ALS is typified instead by a reactive morphology of glial cells, including both astrocytes and microglia (Fig. 1), accompanied by low to moderate levels of inflammatory mediators in the parenchyma. This reaction, both cellular and molecular, is not distinguishable between one disease and another or from other conditions such as stroke or traumatic injury. Given this lack of specificity, it is easy to conclude that the glial reaction is secondary to neuronal death or dysfunction and is accordingly unlikely to provide useful targets for therapeutic intervention or topics for intensive investigation.

It has been several decades since the detection of inflammatory mediators in AD and PD autopsy brain sections led to the proposal that neuroinflammation might promote progression of these disorders (*13*, *14*). Additional support came from a population-based prospective study that used pharmacological records and showed a dose-related negative correlation between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during midlife and the likelihood of later developing AD (*15*). However, subsequent AD treatment trials using NSAIDs, glucocorticosteroids, or selective cyclooxygenase-2 inhibitors failed to provide evidence for efficacy and imposed considerable adverse effects (*16*), leaving inflammation's part in neurodegenerative disease in doubt through the early years of the 21st century.

In this regard, it could until recently be argued that neurodegeneration was mainly a cell-autonomous process affecting neurons. Neurodegenerative disease research advanced the understanding of molecular pathogenesis by identifying selective neuron populations that are affected in each disease. Moreover, there was a potent prima facie plausibility relating the affected cell population with signs and symptoms of the disease, as with neuronal death in the motor system in ALS, in which patients suffer muscle atrophy and weakness. Incisive PD studies using in vitro systems, including the use of somatic cells reprogrammed to become (for example) dopamine neurons, provided support for this hypothesis (*17*).

Demonstrating a non–cell-autonomous neurodegenerative process would open new prospects for understanding how neurodegeneration might be promoted by local CNS inflammation, but it was unclear how to proceed until genetic bases for the Mendelian forms of neurodegeneration were identified and then used to develop in vivo disease models. Dramatic findings came from studying a mouse model of ALS in which the gene encoding mutant superoxide dismutase-1 (mSOD1) was expressed using a ubiquitous promoter, yielding a severe phenotype of motor neuron death with weakness and shortened life span, as observed in humans carrying the same gene variant (*18*). The question was deceptively simple: Did it matter whether the *mSOD1* transgene was expressed in cells other than neurons? Modifying this model to enable inducible deletion of *mSOD1* from all myeloid cells

(represented in the CNS by microglia) produced an unexpected prolongation of life span without altering the timing of disease onset (*19*). A comparable effect was obtained by conditionally deleting *mSOD1* from astrocytes (*20*), and this manipulation also suppressed microglial acquisition of reactive morphology, suggesting a pathogenic scheme by which astrocyte-microglial interactions promoted mSOD1-related neurodegeneration (*21*, *22*). These results showed unequivocally that lack of transgene expression by glia altered the course in the mSOD1 model. Additional positive support for non–cell-autonomous neuronal degeneration came from expression of a mutant α-synuclein transgene selectively in astrocytes, which produced PD-like pathology and behavioral deficits in mice (*23*, *24*). Simultaneously, reports emerged that autopsy tissue sections from cases of PD, PDD, and other diseases associated with aggregated α-synuclein (collectively termed synucleinopathies) featured distinctive aggregates in astrocytes and oligodendrocytes, as well as neuronal Lewy bodies (*25*, *26*).

Unlike neurons, microglia and astrocytes are challenging to study in vitro, partially because they adopt a reactive nonphysiological phenotype upon explant culture, showing a gene expression profile that is markedly different from that of glia when isolated and analyzed immediately ex vivo (*27*). Additionally, the intrinsic functions of glia are exerted in support of neurons within a complex three-dimensional matrix, so that meaningful glial properties cannot be modeled in two-dimensional cultures (*28*). Given this difficulty of using reductionist experimental approaches to evaluate glial neuroinflammatory properties, and in view of the nonspecific nature of cardinal inflammatory changes in glia during neurodegenerative disease, it seems reasonable to propose an all-purpose definition of neuroinflammation in neurodegeneration: contributions by glial cells, elements of the BBB, or systemic inflammatory processes that are harmful or beneficial to the severity of neurodegenerative disease. This broad definition acknowledges the primacy of neurons in brain function and disease and further recognizes that the glial reaction to neuronal injury, dysfunction, or death may be helpful or harmful (or neutral). Additionally, it is proposed that neurodegeneration can progress in a fashion that is non–cell-autonomous with respect to neurons, suggesting that glial biology, the BBB, or the systemic environment all could offer legitimate targets for therapeutic intervention. Moreover, there is no implied similarity to peripheral inflammatory reactions, as demonstrated (for example) by skin or gut macrophages in response to pathogens, because applications of knowledge gleaned from studying peripheral host defense and wound repair have been misleading when applied incautiously to CNS glia (*29*).

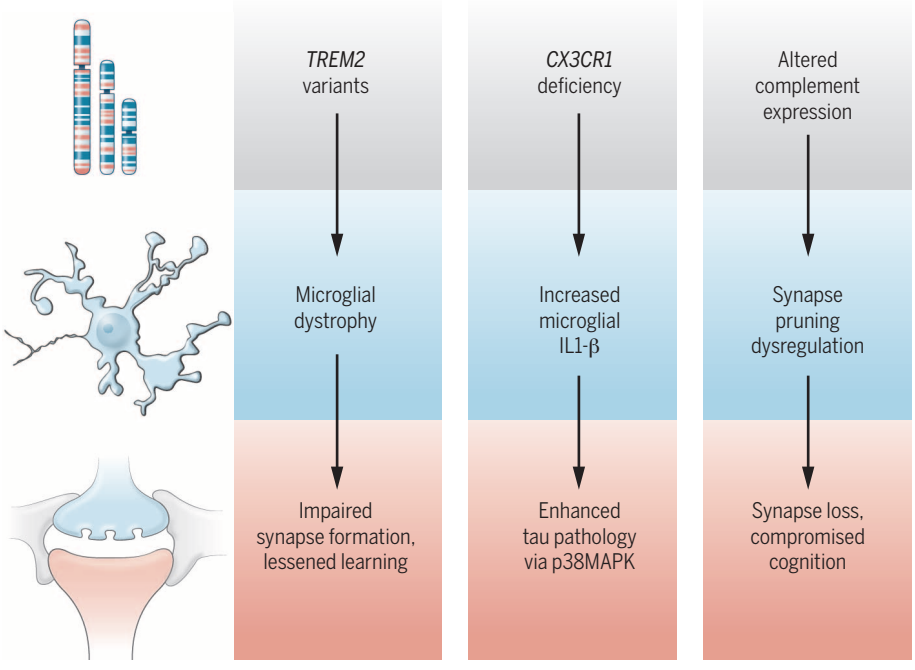

Fig. 2. Pathways from microglial gene variants or altered gene expression to neurodegeneration. *TREM2* variants (*31*), targeted deletion of *CX3CR1* (*70*), and altered complement expression (*77*) have all been associated with neurodegenerative phenotypes in the clinic or in animal models (top row). The middle and bottom rows show the downstream effects. The TREM2 phenotype of microglial dystrophy was studied by means of targeted gene deletion in mice (*78*); the behavioral effect, namely, cognitive deficit in heterozygous *TREM2* haploinsufficiency, was defined clinically (left column) (*79*). Also shown are the neurodegenerative effects of *CX3CR1* deficiency in hTau mice (middle column) (*70*) and complement dysregulation in a model of amyloid pathology (right column) (*77*).

Genetic clues associate neurodegeneration with neuroinflammation

Progress in every domain of biological science has been propelled by genome-level data, and neuroinflammation is no exception. CNS cells involved in neuroinflammatory reactions (microglia, astrocytes, and proteoglycan-NG2$^+$ glia; Table 2) were first identified by their altered morphologies, a descriptive analysis that was unavailing for deciphering whether the cellular reaction was advantageous or deleterious or whether the reaction made any meaningful contribution to pathogenesis. It was therefore a substantial advance to associate Nasu-Hakola disease with homozygous null mutations of *TREM2* (*30*), a gene expressed only by microglia among CNS cells. Despite the extreme rarity of this neurodegenerative disorder, its CNS manifestations of early midlife dementia were unambiguously referable to microglial dysfunction and represented the first evidence that intact microglial activities were essential for brain homeostasis. Relatively subtle *TREM2* genetic variants have now been associated with AD, FTLD, and possibly PD (*31*). Notwithstanding the wealth of *TREM2* coding variants with clinical phenotypes that we can investigate, a mechanistic understanding of why *TREM2* plays such a major role in the risk for neurodegeneration remains contentious and unresolved (*32*) (Fig. 2). Nonetheless, *TREM2* genetics have shown unmistakably that dysfunction of microglia or infiltrating myeloid cells could make a primary rather than a reactive contribution to neurodegeneration and thereby galvanized this field of research. The most salient effects have been found in AD research, where genome-wide association studies (GWAS), supplemented by examination of rare variants and identification of expression quantitative trait loci in microglia, have identified about 20 well-validated genes harboring risk alleles, of which about half are predominantly or only expressed in microglia (*33*). For example, *APOE*, the dominant risk-associated gene, is mainly expressed in astrocytes and reactive microglia (*34*). The availability of convenient, searchable, brain cell–specific databases of RNA-sequencing and microarray expression profiles enables the pursuit of this research direction (*34*–*36*).

In P-MS, inflammation begets neurodegeneration—but how?

MS is relatively common (prevalence of 1:1000) among susceptible populations. Onset occurs at about age 30, with two-thirds of affected individuals being women. Life is only modestly shortened by MS; the disease course is about 45 years. In its early phases of clinical presentation, MS is distinctive, which led to its characterization as a discrete disease entity more than 150 years ago. Patients experience abrupt (minutes to hours) or subacute (days to weeks) alterations in neurological function, termed attacks or relapses. In its early phase, MS remains a disturbing but not disabling disease for many patients, about 85% of whom present with the relapsing form of the disease. Relapses occur from time to time,

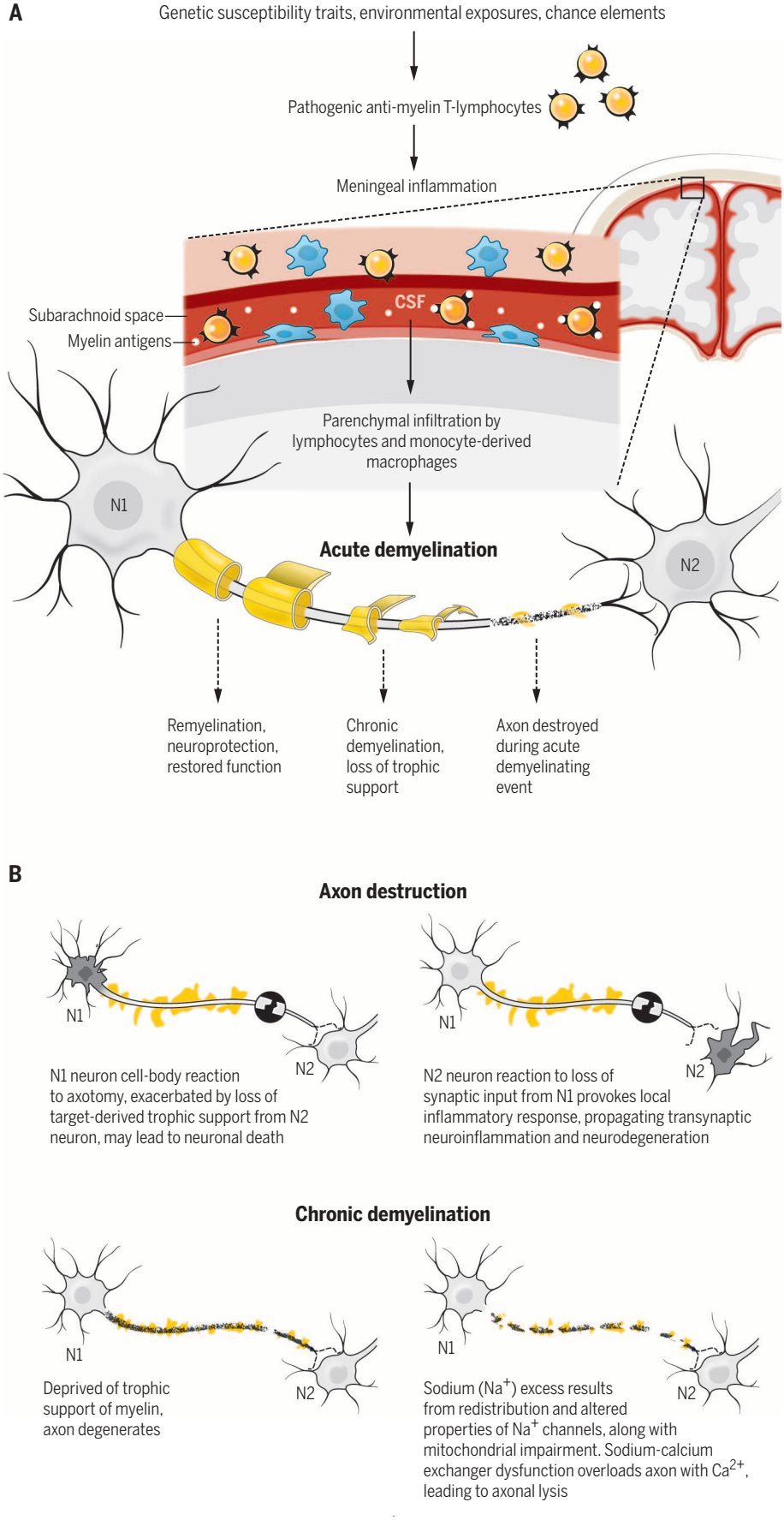

Fig. 3. Pathogenesis of neurodegeneration in P-MS. (**A**) Pathogenesis and short-term outcomes of acute demyelination. N1 is a neuron, shown extending an axon to synapse with neuron N2. The axon is myelinated (yellow shapes). In MS, generation of pathogenic antimyelin T cells results from gene-environment interactions, supplemented by yet-to-be-identified chance elements (*80*–*82*). Pathogenic T cells traffic through cerebrospinal fluid (CSF) and can be restimulated by myelin antigens in the subarachnoid space (*83*) to initiate meningeal inflammation (*41*); this is followed by parenchymal invasion by T cells and monocyte-derived macrophages, which mediate demyelination. Potential alternative outcomes of acute demyelination are shown at the bottom. (**B**) Outcomes of acute axotomy during demyelination and of chronic demyelination. Acute axotomy (top) causes a stereotyped cell-body reaction for neuron N1. Contingent on the proximity of the axotomy to the neuron cell body and the loss of trophic support from N2, this reaction may lead to the death of the N1 neuron. Additionally, removal of synaptic input can produce an intense local inflammatory reaction around the N2 target neuron (*84*) as glia sense the change in neuronal function. Chronic demyelination (bottom) deprives axons of essential trophic support, threatening their viability and producing susceptibility to axon degeneration (*85*). Furthermore, chronic demyelination causes redistribution of sodium (Na^+) channels away from nodes of Ranvier into the demyelinated segment, as well as altered channel expression (*86*), worsening the risk of Na^+ overload. Axonal conduction produces a Na^+ influx that is poorly balanced by Na^+- and K^+-dependent adenosine triphosphatase, which is impaired as a result of mitochondrial dysfunction (*87*). Sustained Na^+ overload reverses the Na^+-Ca^{2+} antiporter, and the resulting Ca^{2+} influx activates calcium-dependent enzymes, lysing the axon.

with substantial or complete resolution, and attacks leading to permanent disability are more the exception than the rule. MS patients exhibiting this disease pattern are said to have relapsing-remitting MS (RR-MS). Importantly, neurological function, as experienced by patients and assessed by neurologists, remains stable between relapses. Among all CNS diseases [except for neuromyelitis optica (NMO), an autoimmune astrocytopathy], MS is distinctive by virtue of its recurrent (multiphasic) and regionally diverse (multifocal) symptoms, punctuated by periods of symptomatic quiescence. The recurrent nature of MS is most likely due to cellular autoimmunity to myelin that drives the disease.

After a variable period of RR-MS, the disease appears to change its behavior. Attacks become much less common and may cease altogether, to be replaced by a progressive phase during which patients slowly and often relentlessly worsen, without periods of symptom reversal or improvement. This pattern of symptom evolution is designated secondary P-MS. In about 10% of cases, MS presents with progression from the onset, lacking the earlier phase of attacks and remissions. It seems most likely that this symptom pattern,

termed primary P-MS, represents the sequelae of typical MS lesions that were clinically silent during the inflammatory phase of disease (*37*, *38*). However, recurrent longstanding neuroinflammation does not inevitably lead to neurodegeneration: In NMO, the other major inflammatory disease of the human CNS, which is caused by autoantibody-mediated astrocytopathy directed at aquaporin-4, there is no progressive phase for the vast majority of patients.

There is a coherent hypothesis to account for neurodegeneration after inflammatory demyelination in MS (Fig. 3). In this view, the sequelae of acute demyelination can lead to progressive loss of axons and neurons unless robust remyelination occurs, which happens in a subset of MS cases (*39*, *40*). In addition to these cellular sequelae of demyelination that produce neurodegeneration in MS, meningeal inflammatory infiltrates are established at the earliest stages of disease (*41*, *42*) and continue to be detectable during clinical progression (*43*), remaining readily observable at autopsy (*44*). Tissue studies (*41*, *44*) and magnetic resonance imaging–pathological correlations (*43*) support the likelihood that these intrathecal inflammatory foci drive ongoing demyelination of underlying cortical tissue.

Which neuroinflammatory treatment target for which disease?

The study of the neuroinflammatory aspects of neurodegeneration is now in a "good news–bad news" situation. Genetic, epidemiological, and descriptive research using brain tissue from patients—as well as results from model systems including genetically modified mice, zebrafish, flies, worms, and induced pluripotent stem cells (iPSCs), which harbor disease-associated genetic variants in the native genomic context—forcefully implicate inflammation in the neurodegenerative process. As one example, mice lacking progranulin, which is encoded by *Grn* and expressed predominantly in the microglia of both humans (*34*) and mice (*36*), showed substantial dysregulation of microglial complement gene expression and of lysosome maturation. These findings were associated with evidence of unexpectedly selective and regionally restricted loss of inhibitory vesicular GABA (γ-aminobutyric acid) transporter–labeled synapses of parvalbumin-positive neurons in the ventral thalamus, where complement deposition was observed on both excitatory and inhibitory synapses. In turn, aged $Grn^{-/-}$ mice exhibited altered thalamic excitability and excessive grooming. The relationship to complement gene expression was established by showing substantial phenotypic rescue in $Grn^{-/-}$::*C1qa*$^{-/-}$ mice (*45*). These findings are exciting because of the demonstration that a specific neuronal circuit can be functionally derailed through complement- and microglial-mediated synapse removal. At the same time, several issues were not addressed, including the relation of the phenotype to loss of progranulin as opposed to loss of granulin peptides (derived by proteolysis from progranulin); how complement dysregulation leads to selective synapse loss, given that deposition does not discriminate excitatory from inhibitory synapses; the role (if any) of lysosomal trafficking in the phenotype; and signaling pathways underlying altered microglial gene expression (*45*). Overall, this study advances our understanding of progranulin deficiency while standing in continuity with other studies showing that specific neuroinflammatory genes or pathways are plausibly associated with AD, PD, and ALS. Nonetheless, no therapeutics have emerged from this line of research. There are reasonable explanations for this circumstance, including the inherent complexity of neurodegenerative disease, challenges related to clinical trial design, and lack of actionable high-throughput screening platforms (particularly as regards cultured glial cells), among others. For now, the following strategic formulations to address these issues may be useful.

"...neurodegeneration can progress in a fashion that is non-cell-autonomous with respect to neurons, suggesting that glial biology, the BBB, or the systemic environment all could offer legitimate targets for therapeutic intervention."

Genetics are key

Target identification based on human-disease genetic validation enhances prospects for success. GWAS loci have proven to be robustly reproducible, and the initial threshold for genome-wide significance appears durable (*46*). Proceeding from loci to genes to pathways remains challenging, but methods for confirming "hits" are highly promising. Systems biology can make additional contributions to target prosecution.

Remain unbiased even after the omics are done

Confronted with an uncertain comprehension of neurodegenerative disease, it is tempting to rely on dogma. Deciphering inflammation has been challenging, even in the familiar context of adaptive-immune disorders such as rheumatoid arthritis. Innate immunity in the CNS is an unfamiliar landscape in which well-known actors and their properties may be upended. One example comes from considering neuroprotective properties of TNF-α (tumor necrosis factor–α) and the associated NF-κB (nuclear factor κB) signaling pathway (Table 2).

New models will be needed

In vitro cultures of glial cells have been poorly predictive of relevant activities and phenotypes in vivo (*28*). Novel systems including organotypic brain-slice cultures (*47*), zebrafish (*48*), and iPSCs (for astrocytes) (*49*) are required.

Consider the periphery

Glial cell phenotypes are modulated profoundly by peripheral inflammatory stimuli (*50*), including dysbiosis due to altered gut microbiota (*51*, *52*), findings which have been confirmed in clinical studies (*53*). Compared with direct manipulation of CNS cells or factors, manipulating the peripheral environment to modulate neurodegenerative disease would be manifestly less encumbered by concerns about safety, biomarker selection, or off-target effects. This consideration also pertains directly to the potential role of the BBB in neurodegeneration (*54*, *55*), which was highlighted by the finding that access of blood-borne pathogens to the CNS in the context of a compromised BBB might stimulate amyloid deposition (*56*).

Conclusions and future prospects

The study of neuroinflammation as a major contributor to neurodegeneration is, in some ways, fewer than two decades old, dating from the demonstration that altered microglia produce a neurodegenerative phenotype in humans (*57*). This line of research encompasses disease-related alterations in the environment in which neurons exist, including those coming from glial reaction to the disorder, as well as intra-CNS effects of peripheral inflammatory stimuli and the degradation of homeostasis caused by an impaired BBB. Available research resources such as genomic and epigenetic data sets, model organisms, and iPSC-derived cells enable an unprecedented scope of research attack. Given these circumstances, neuroinflammation researchers should be cognizant of the task's complexity and previous defeats, while approaching with cautious optimism the prospect of therapeutic success against these severe diseases.

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PERSPECTIVE

Inflammatory neuroprotection following traumatic brain injury

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Traumatic brain injury (TBI) elicits an inflammatory response in the central nervous system (CNS) that involves both resident and peripheral immune cells. Neuroinflammation can persist for years following a single TBI and may contribute to neurodegeneration. However, administration of anti-inflammatory drugs shortly after injury was not effective in the treatment of TBI patients. Some components of the neuroinflammatory response seem to play a beneficial role in the acute phase of TBI. Indeed, following CNS injury, early inflammation can set the stage for proper tissue regeneration and recovery, which can, perhaps, explain why general immunosuppression in TBI patients is disadvantageous. Here, we discuss some positive attributes of neuroinflammation and propose that inflammation be therapeutically guided in TBI patients rather than globally suppressed.

Traumatic brain injuries (TBIs) cause many reactions; one of the most prominent is neuroinflammation. Damage to the CNS elicits inflammatory responses from resident microglia and macrophages, as well as peripheral immune cells, such as neutrophils, monocytes, and T cells. Microglia and resident macrophages immediately respond to injury after sensing damage-associated molecular patterns (DAMPs), such as the presence of adenosine triphosphate (ATP) or intracellular proteins that are released from damaged or dying cells. Signaling from DAMP receptors initiates local cytokine and chemokine production, which affects the immediate environment and provides a cue for peripheral immune infiltration (*1*). A major question in the field of TBI research is how the immune response influences the pathogenesis of brain injury and recovery. Although a number of studies suggest that neuroinflammation is detrimental and inhibitory to neural regeneration following TBI, the failure of anti-inflammatory drugs to achieve a therapeutic benefit in human clinical trials supports a growing need to more carefully interrogate the duality of TBI-induced immunity. Immune reactions do indeed have the means to cause damage, but they also play a critical role in promoting tissue repair and recovery following brain injury.

Pathogenic inflammation following TBI

Microglia are resident immune sentinels that respond to nearly all inflammatory events within the CNS. Their exact contribution to the pathogenesis of brain injuries is not entirely understood, but studies have shown that microglial activation can persist for years following TBI in humans (*2*). For example, analysis of microglia and associated pathology in TBI patients revealed clusters of activated microglia (evidenced by CR3 and CD68 immunoreactivity) in 28% of patients that survived for more than 1 year after a single brain injury (*2*). These patients also showed active signs of white matter degeneration, indicative of a chronic pathological process. However, it is unclear whether microglia are active participants in this prolonged degenerative process or are simply responding to the pathology induced by other mechanisms. Investigators have attempted to interrogate microglia in animal models of TBI, although the results are not definitive. Minocycline is an antibiotic with anti-inflammatory properties that is commonly used to suppress microglia and/or macrophage activation. This compound showed some therapeutic benefit (i.e., reduced microglia activation and brain lesion size) in a weight drop model of TBI (*3*), but the improvement cannot be linked exclusively to the effect of minocycline on microglia. Another study similarly concluded that microglia are pathogenic by studying cortical injury in the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-2 $(NOX2)^{-/-}$ mice (*4*). NOX2 is a subunit of NADPH oxidase expressed by activated microglia and known to generate reactive oxygen species (ROS). Both ROS production and lesion sizes were reduced in injured $NOX2^{-/-}$ mice, which suggested that microglia-derived ROS exacerbates TBI damage (*4*). Because the mice in this study were globally deficient in NOX2, it will be important in future studies to link pathogenic NOX2 activity exclusively to microglia.

"At least some inflammation may be necessary in the acute stage of CNS injury to clear damage and set the stage for remodeling efforts."

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