Neurotroxic vs neuroprotective Glia functions

Neurotoxic Glia

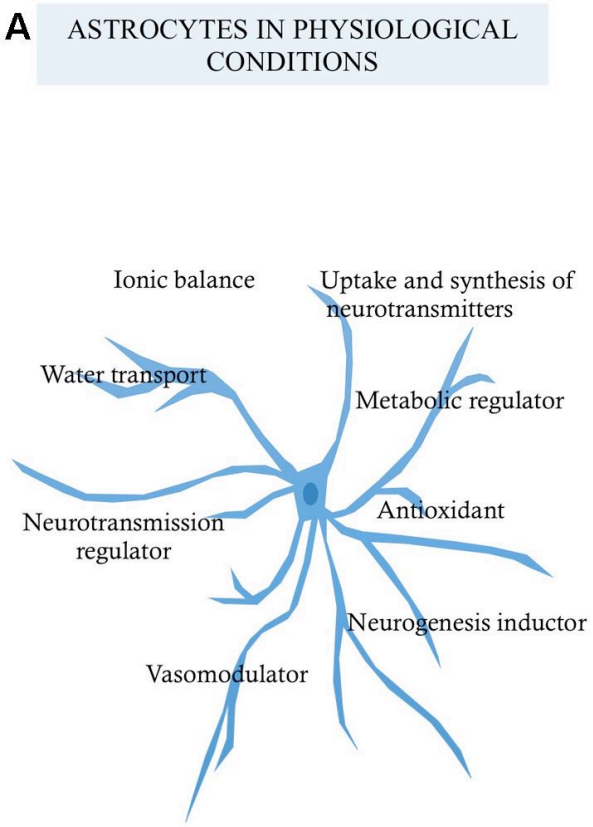
Types of neurotoxicity

- Microglia — neurotoxic cytokine release
  ROS

- Astrocytes — astrogliosys, Glu uptake reduction
  Glu, tumorigenesis

Astrocytes

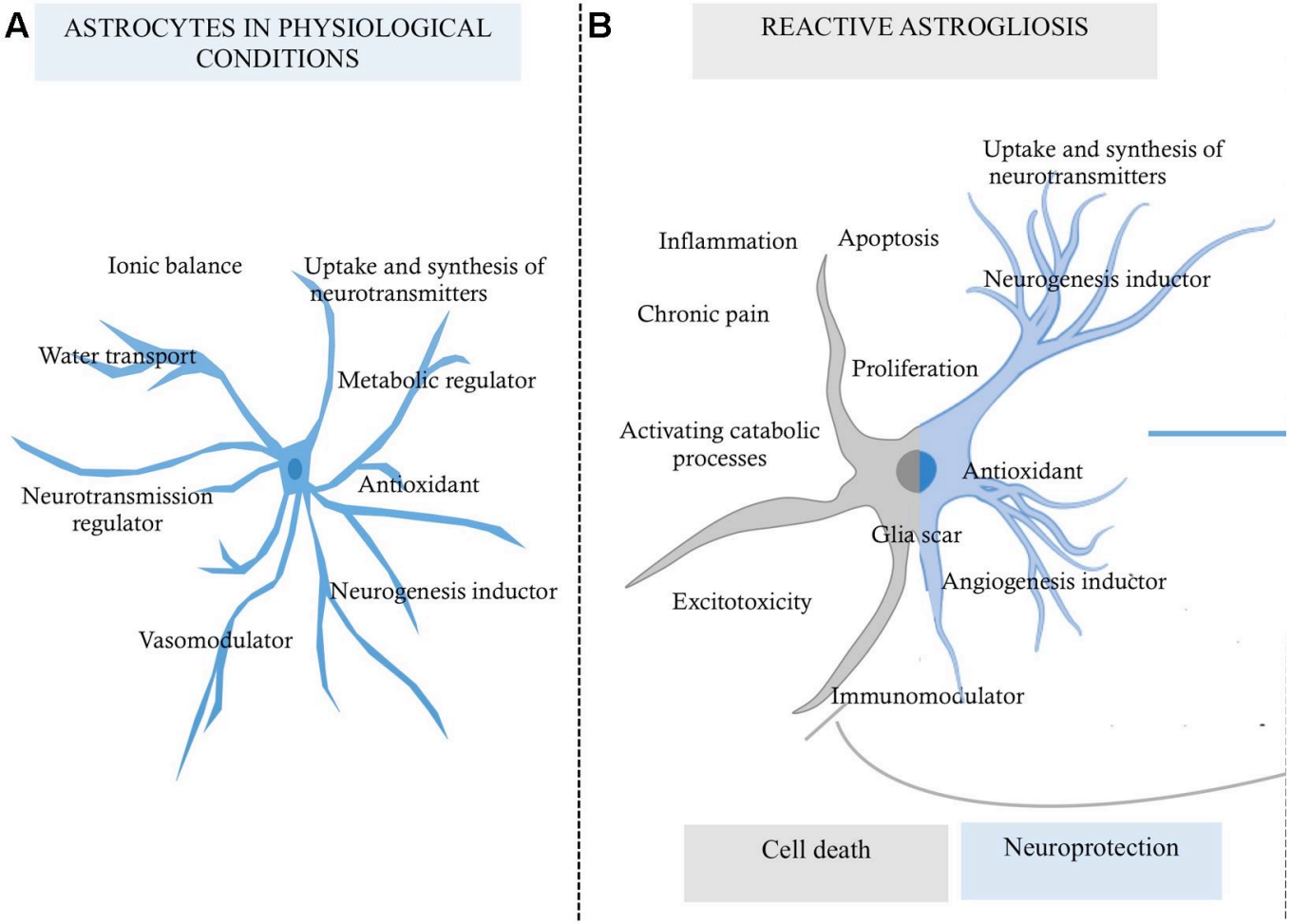
Role of astrocytes in a micro-environment dependent-mode.



Functions of the astrocytes in physiological conditions, which are in favor of the homeostasis of the nervous tissue.

Astrocytes

Role of astrocytes in a micro-environment dependent-mode.

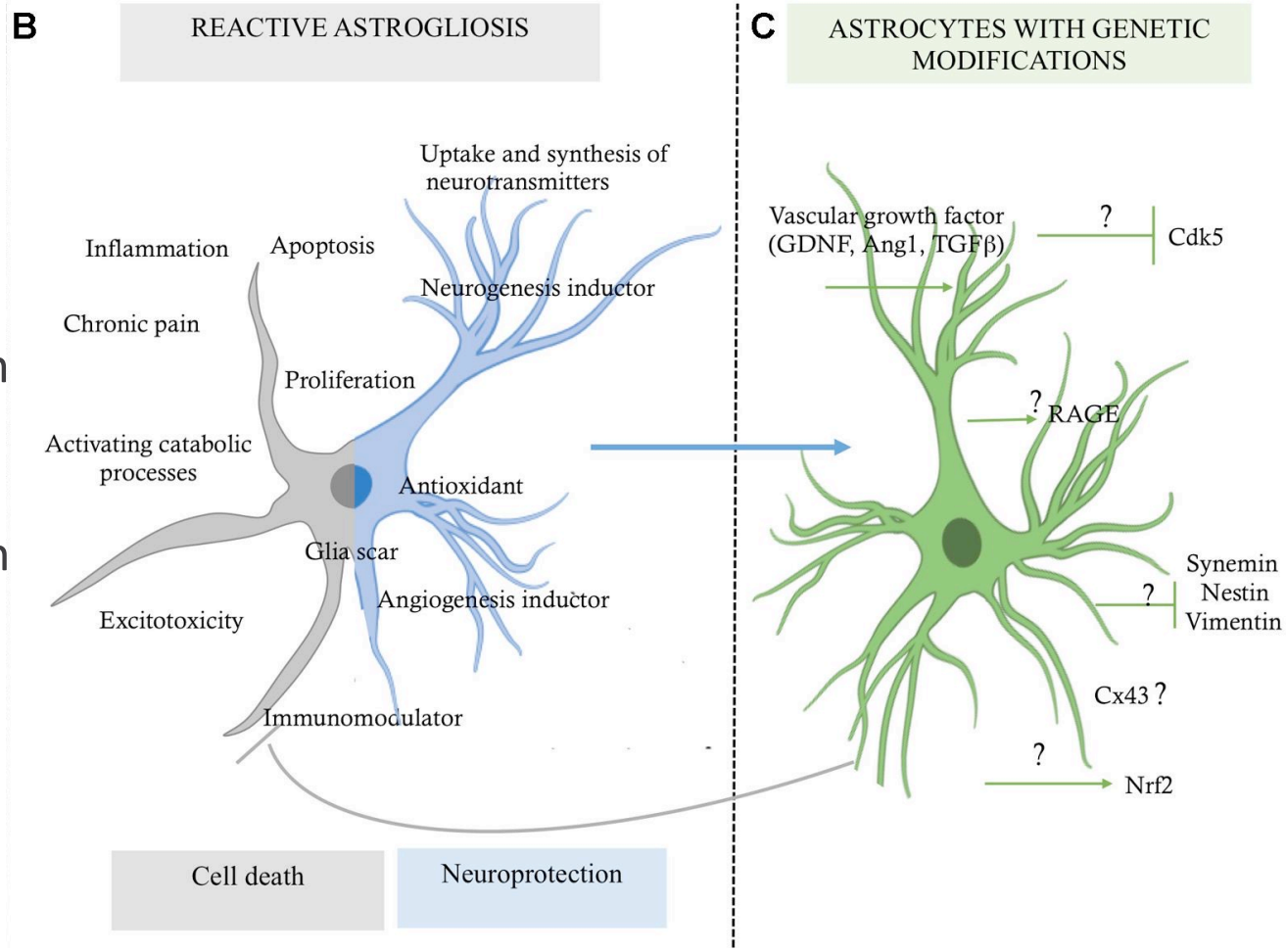


Reactive astrocytosis, which has a double function highly discussed, one for cell death and one for pro-neuroprotection probably in a context dependent-mode.

Astrocytes

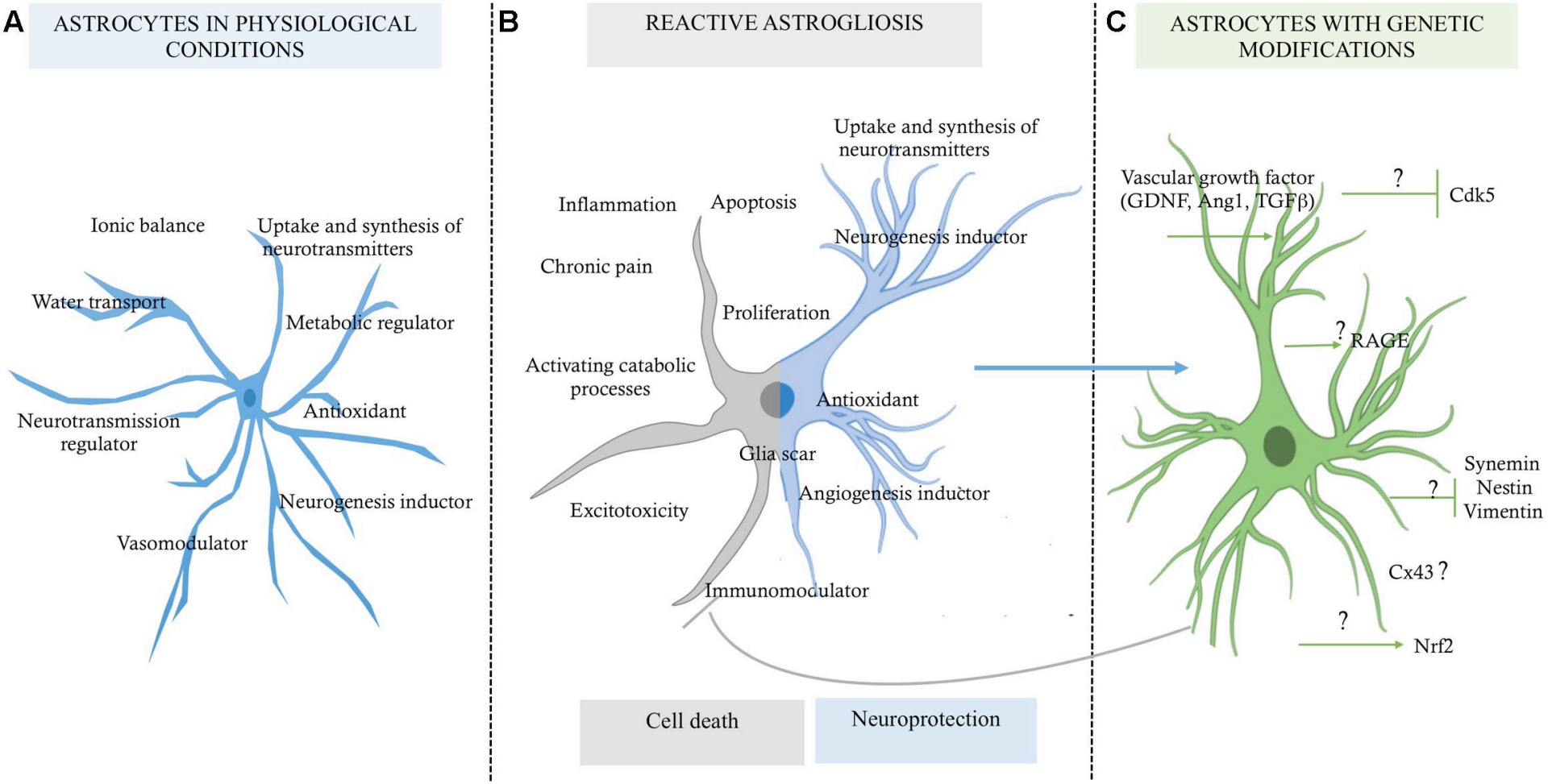
Role of astrocytes in a micro-environment dependent-mode.

Astrocytes with genetic modifications by reduced expression of some upregulated genes, which would allow preserve them as a neuroprotective source for promoting neuronal survival; although the mechanism of how they could maintain this state of neuroprotection for longer time is still unknown (?).



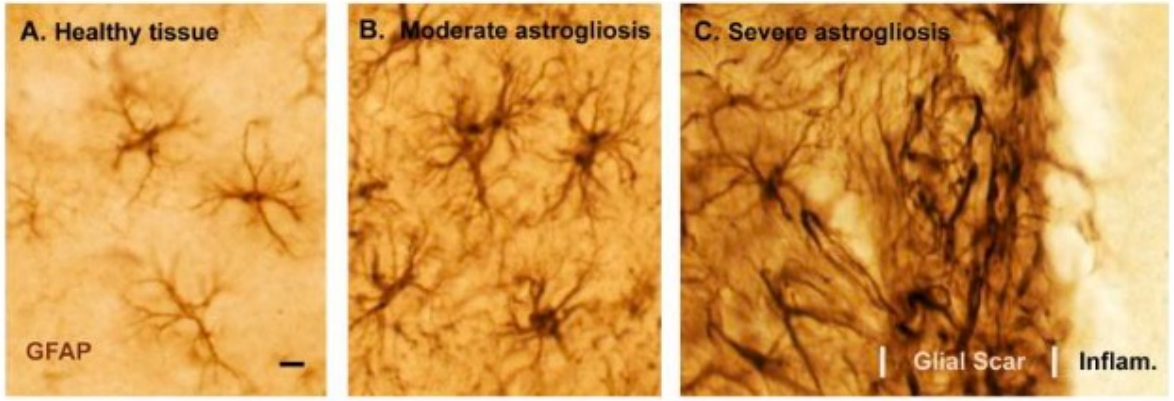
Astrocytes

Role of astrocytes in a micro-environment dependent-mode.



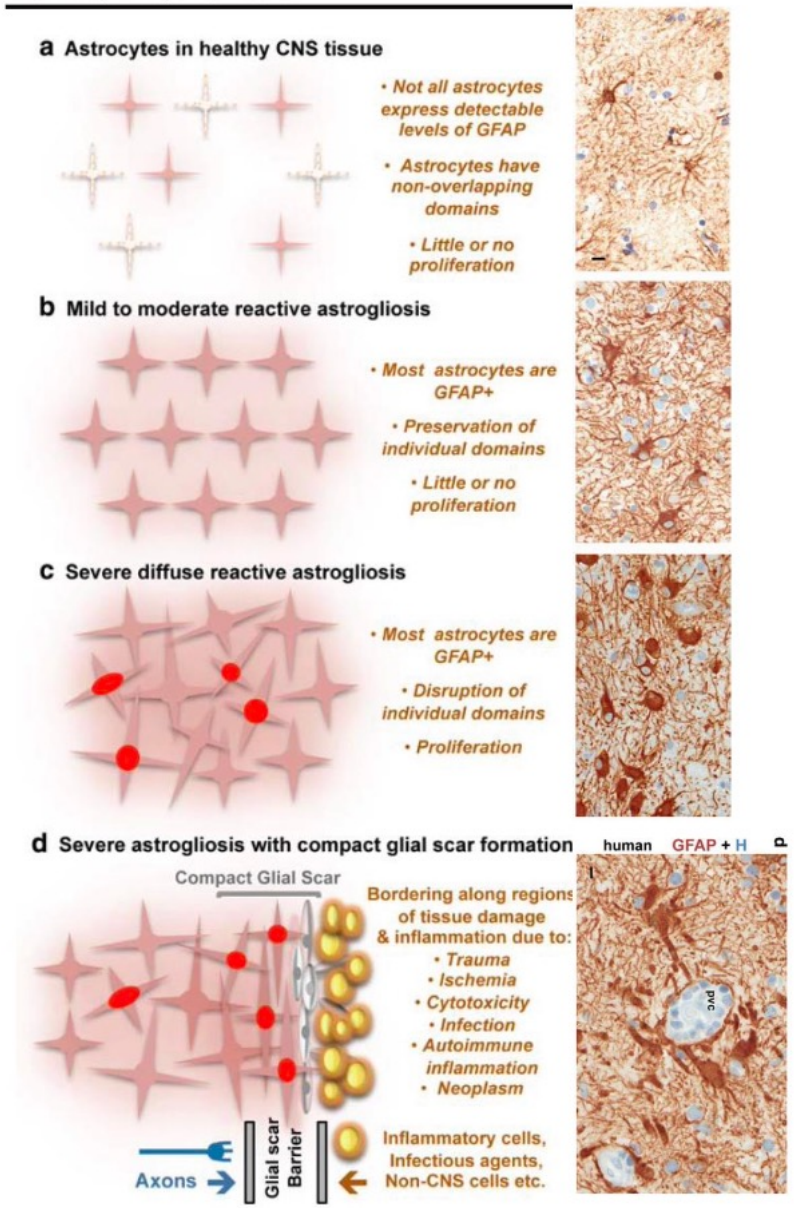
Astrocytosis

- Astrocytosis/gliosis: response of astrocytes to many forms of injury: trauma, inflammation, MS, infection, neurodegeneration
- Classical description of gliosis is hypertrophy, glial filament production +/- proliferation.
- Reality: there must be many distinct forms of astrocyte activation; hundreds or thousands of distinct changes in gene expression



Astrocytosis

Acta Neuropathol (2010) 119:7–35



Different grades of reactive gliosis

Fig. 4 Schematic representations that summarize different gradations of reactive astrogliosis. **a** Astrocytes in healthy CNS tissue. **b** Mild to moderate reactive astrogliosis comprises variable changes in molecular expression and functional activity together with variable degrees of cellular hypertrophy. Such changes occur after mild trauma or at sites distant from a more severe injury, or after moderate metabolic or molecular insults or milder infections or inflammatory activation. These changes vary with insult severity, involve little anatomical overlap of the processes of neighboring astrocytes and exhibit the potential for structural resolution if the triggering insult is removed or resolves. **c** Severe diffuse reactive astrogliosis includes changes in molecular expression, functional activity and cellular hypertrophy, as well newly proliferated astrocytes (with *red* nuclei in figure), disrupting astrocyte domains and causing long-lasting reorganization of tissue architecture. Such changes are found in areas surrounding severe focal lesions, infections or areas responding to chronic neurodegenerative triggers. **d** Severe reactive astrogliosis with compact glial scar formation occurs along borders to areas of overt tissue damage and inflammation, and includes newly proliferated astrocytes (with *red* nuclei in figure) and other cell types (*gray* in figure) such as fibromeningeal cells and other glia, as well as deposition of dense collagenous extracellular matrix. In the compact glial scar, astrocytes have densely overlapping processes. Mature glial scars tend to persist for long periods and act as barriers not only to axon regeneration but also to inflammatory cells, infectious agents, and non-CNS cells in a manner that protects healthy tissue from nearby areas of intense inflammation

Sofroniew & Vinters, 2010
Acta Neuropathol
DOI 10.1007/s00401-009-0619-8

Astrocytosis

Astrogliosis in cerebro-vascular deseases

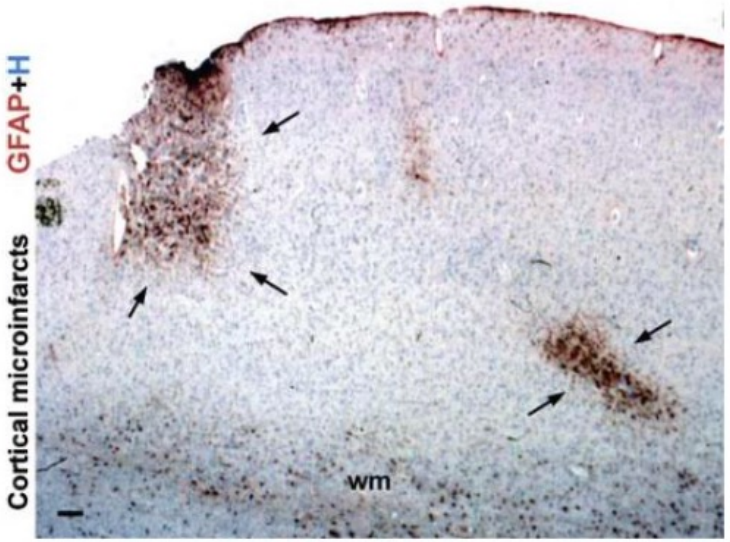


Fig. 5 Reactive astrogliosis demarcates cerebral microinfarcts. Survey image of cerebral cortex of an elderly individual showing microinfarcts (*arrows*) highlighted by dense clusters of prominently reactive astrocytes that stain intensely for GFAP. Fibrous astrocytes within subcortical white matter (*wm*) exhibit GFAP staining, whereas GFAP is not detectable in most protoplasmic gray matter astrocytes remote from the lesions in this specimen. *H* haematoxylin counterstain. *Scale bar* 180 µm

Sofroniew & Vinters, 2010
Acta Neuropathol
DOI 10.1007/s00401-009-0619-8

Astrogliosis in Alzheimer desease

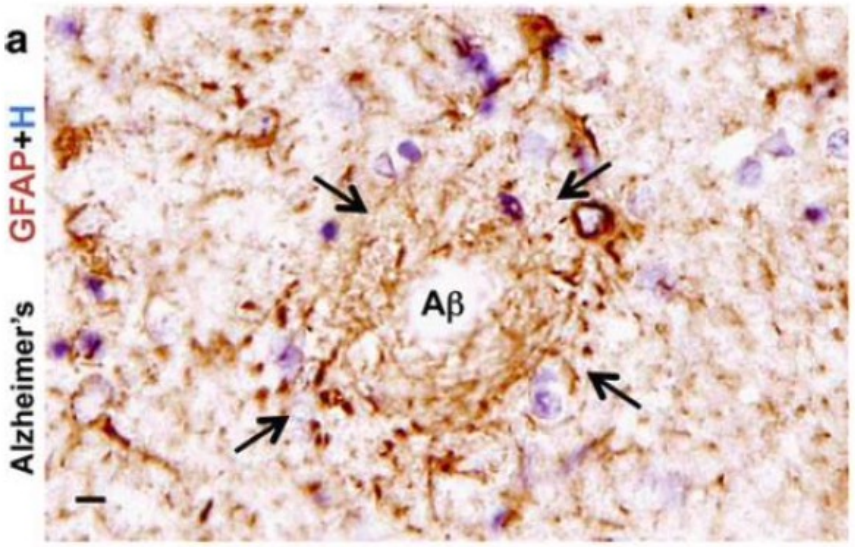
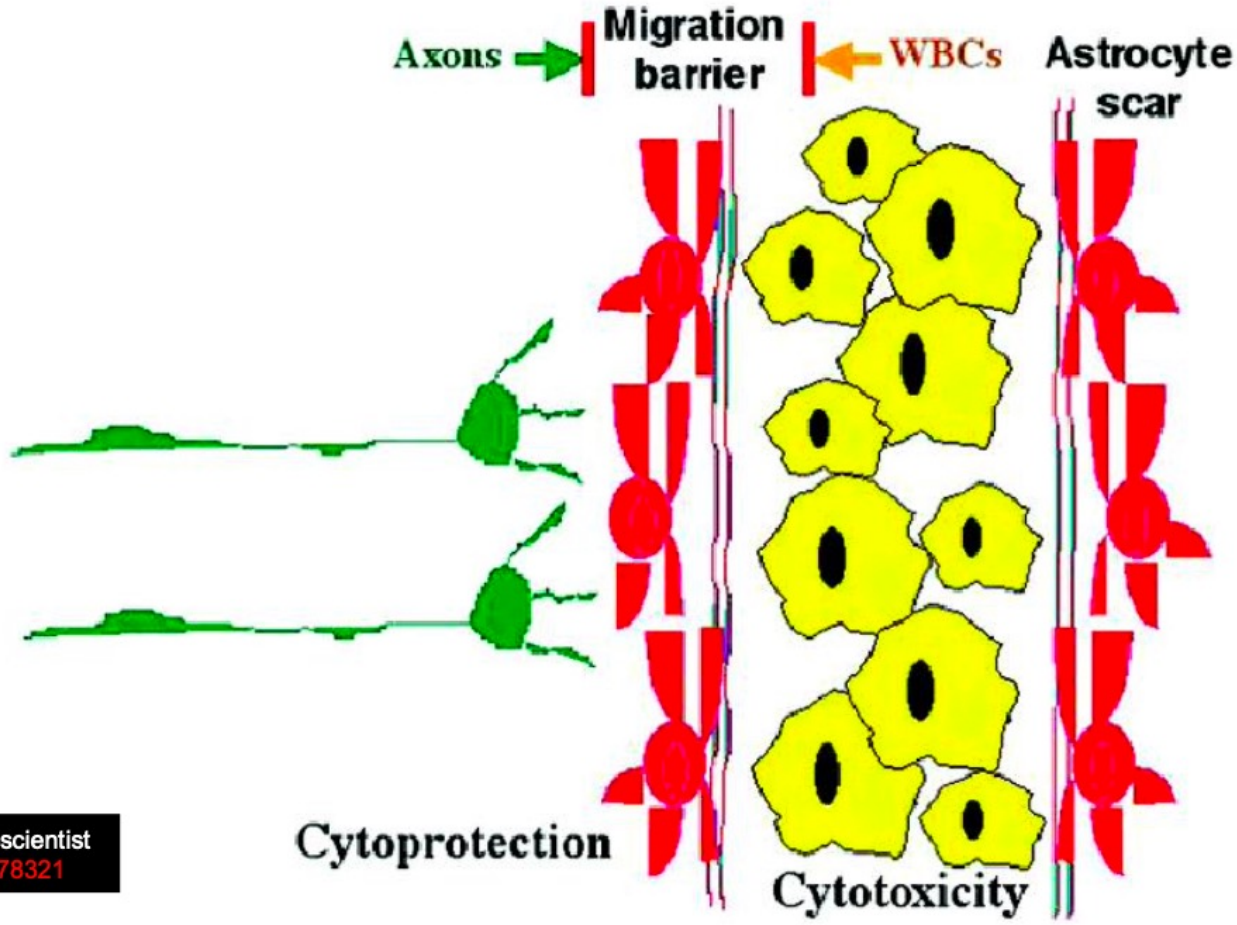


Fig. 7 Reactive astrogliosis in two degenerative diseases. **a** High magnification image of autopsy specimen from a person with longstanding Alzheimer's disease immunohistochemically stained for GFAP. Section of cerebral cortex shows an amyloid senile plaque with a pale unstained center (Aβ) ringed by dense layers of reactive astrocytic processes (*arrows*) that circumferentially surround the plaque as if forming a scar-like barrier around it. **b** High magnifi-

Astrocytosis

Astrocytic scar: good or bad?



Sofroniew, 2005, The Neuroscientist
DOI: 10.1177/1073858405278321

Fig. 4. Schematic of barrier functions of scar-forming reactive astrocytes. Scar tissue organized by reactive astrocytes walls off areas of compromised tissue. Within the walled-off area, a robust inflammatory reaction occurs with the release of potent cytotoxic agents targeted at potential invading microorganisms, but that also sacrifices local neural cells. Outside of and immediately adjacent to the astrocyte scar, inflammation is minimal and cytoprotective mechanisms are active. Although the astrocyte scar may serve primarily as a migration barrier that keeps inflammatory white blood cells (WBCs) from invading adjacent healthy tissue, the redundancy of migratory guidance cues among neurons and leukocytes may account for the inhibition of axon regeneration by this barrier.

Astrocytosis

Brain Injury and Reactive Astrogliosis

- ~ 24 - 48 hr →
- Hypertrophy & Proliferation
- ↑ expression of GFAP
- Isolate the lesion

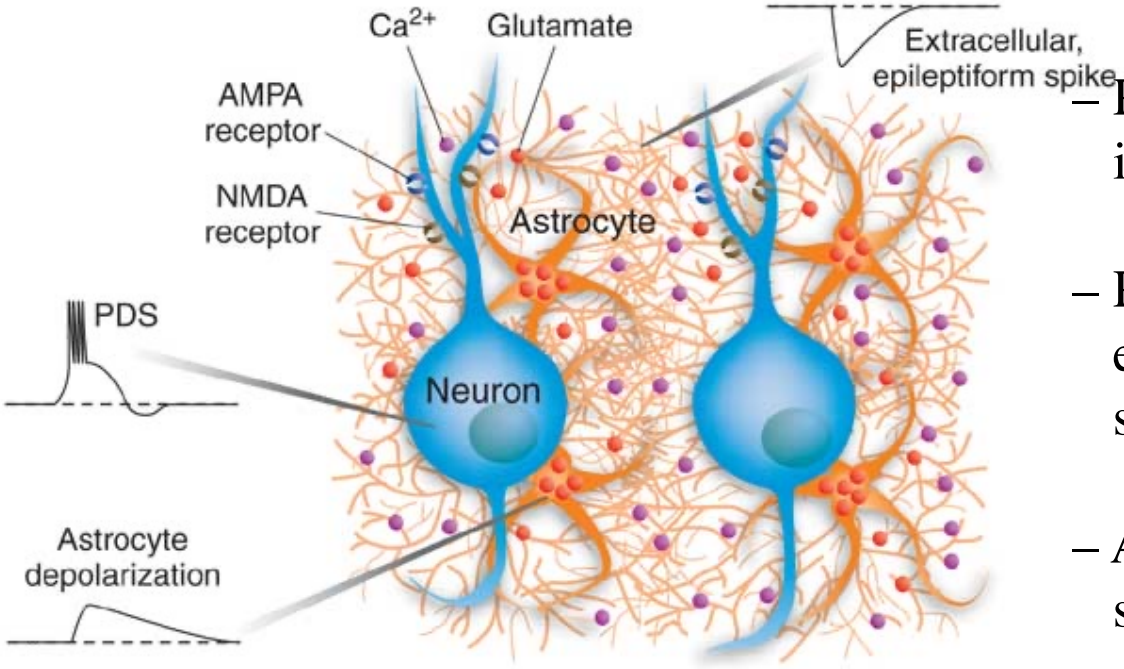
Reactive astrocytes may have a beneficial effect

Buffering extracellular K+
Removing excess glutamate
Repair of the extracellular matrix
Reestablishing BBB integrity
Provide trophic support for neurons
Reduce inflammatory response

Astrocytes and Epileptic Seizures

Tian et al.:*An astrocytic basis of epilepsy* (Nature Medicine, 11 (2005)

Epileptic discharges through local paroxysmal depolarization shift (PDS) driving groups pf neurons into synchronous bursting activity.



-- Ca2+ increased in Astrocyte

– PDS - like epileptiform responses in neighboring neurons

– PDS in nearby neurons in in-vitro epilepsy models with blocked synaptic transmission

– Anti-epileptics reduced Ca2+ signal in astrocyte

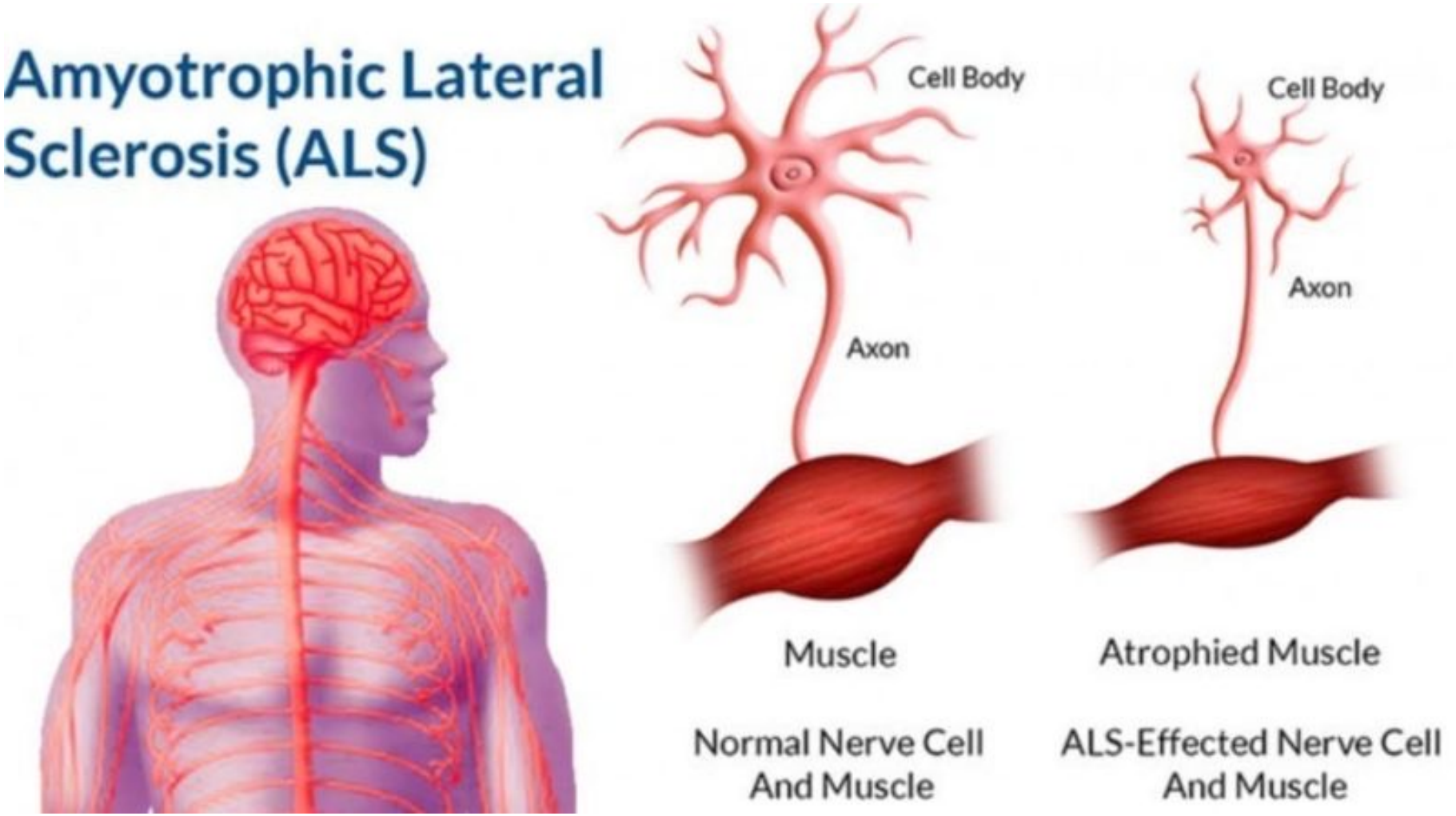
Epilepsy and astrocytes

– in astrocytes from epileptic foci mGluRs are overexpressed by a factor of about 20 (rat models and human) (Ulas et al., Glia 30, 352 (2000), Tang and Lee, J. Neurocytology, 30, 137 (2001), Aronica et al. Europ.J. Neurosci., 12, 2333 (2000),

– Enhanced IP_3 Hydrolysis and increased Ca^{2+} spikes during epileptic seizure (Ong et al. J. Neurochem. 72, 1574 (1999)

– More spontaneous astrocytic calcium spikes in epileptic (Tashiro et al., J. Neurobiol. 50, 45 (2002)

Amyotrophic Lateral Sclerosis (ALS)



Amyotrophic Lateral Sclerosis (ALS)

Introduction to ALS

Amyotrophic lateral sclerosis (ALS), first described in the 19th century, is a progressive, presently incurable neurodegenerative disorder that causes muscle weakness, disability, and eventually death. ALS is also known as **Lou Gehrig's disease**, after the famous NY Yankee baseball player affected with the disorder.

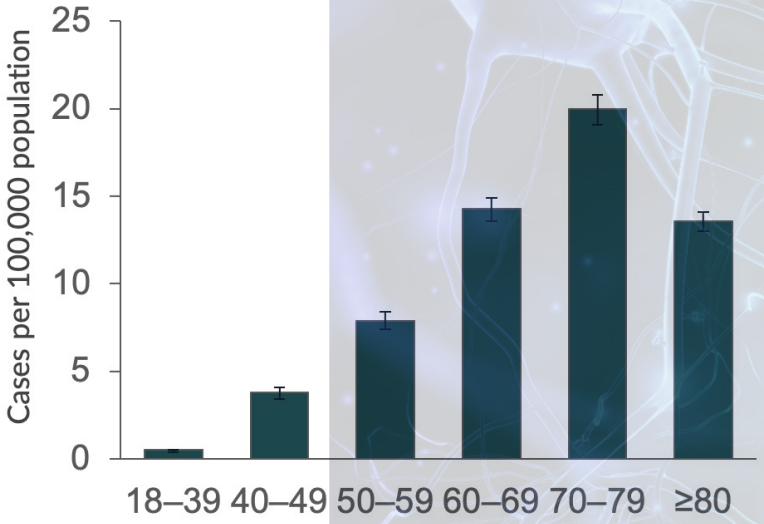
Incidence

- **1.5 to 2.7** cases per 100,000 people/year in Europe and North America[1,2]
- In the US, ALS rates are higher among whites compared with other races[3,4]

Prevalence

- **2.7 to 7.4** cases per 100,000 people/year in Europe and North America[4,5]

Prevalence estimate by age[4]



1. Jordan, Rechtman et al. 2015. **2.** Logroscino, Traynor et al. 2010. **3.** Roberts, Johnson et al. 2016. **4.** Mehta, Kaye et al. 2018. **5.** Byrne, Walsh et al. 2011.

Amyotrophic Lateral Sclerosis (ALS)

Risk factors and genetic causes

Age and smoking

Age[1] and family history are the only established risk factors for ALS

Accumulating evidence implicates cigarette smoking as a risk factor for ALS[2-4]

Genetic Susceptibility

- About 5% of all ALS cases are inherited (fALS) in a Mendelian inheritance pattern[5]
  - Genetics explain about 61% liability in ALS even in patients with no family history[6]
  - Patients with sporadic ALS show mutations in genes associated with fALS
- Variations in more than 40 different genes and loci appear to be associated with ALS susceptibility[7]
  - Known fALS genes include: ***C9ORF72*** *(>20%),* ***SOD1*** *(13-20%)*, *TARDBP*, *FUS*, *ANG*, *OPTN*, *SETX*, and *SQSTM1*
  - The most common ALS mutation in European patients is the *C9orf72* repeat expansion; mutations in *SOD1* are the most common mutations in Asia[5]
  - Susceptibility genes not associated with fALS include: *TBK1*, *ATXN2*, *C21ORF2*, *ITPR2*, and *NEK1*[8] genes, and duplications in the *SMN1* gene

Amyotrophic Lateral Sclerosis (ALS)

Prognosis

Survival characteristics of the disease

- Most ALS patients die within 3 to 5 years of diagnosis
- ~30% of ALS patients are alive 5 years after diagnosis, and 10-20% survive for >10 years
- Survival beyond 20 years is rare, but possible, and depends in part upon treatment decisions made by patients and their families
- Factors associated with more favorable survival[1-4] include:
  - Younger age at symptom onset
  - Limb rather than bulbar symptom onset

Presenting features associated with prolonged survival in ALS

- Prolonged time from onset to diagnosis
- Younger age of onset
- Pure UMN signs
- Pure LMN signs
- No dyspnea at onset
- Nonbulbar region of onset
- Normal weight/nutrition status at diagnosis
- Nonfamilial ALS
- Normal cognition at diagnosis

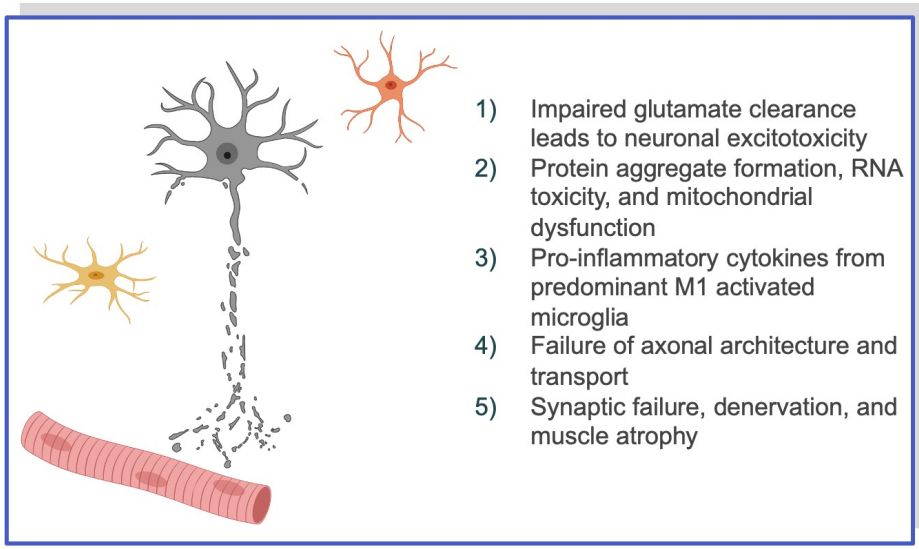
Amyotrophic Lateral Sclerosis (ALS)

Mechanism of disease

ALS is characterized by:

- Motor neuron degeneration and death with gliosis replacing lost neurons
- Loss of cortical motor cells (pyramidal and Betz cells), leading to retrograde axonal loss and gliosis in the corticospinal tract
- Spinal cord atrophy
- Thinning of ventral roots
- Loss of large myelinated fibers in motor nerves
- Denervation atrophy of affected muscles with evidence of reinnervation such as fiber type grouping
- Intracellular inclusions in degenerating neurons and glia

Molecular mechanisms in the pathology of ALS



Adapted from[1]

1. Ciervo, Ning et al. 2017.

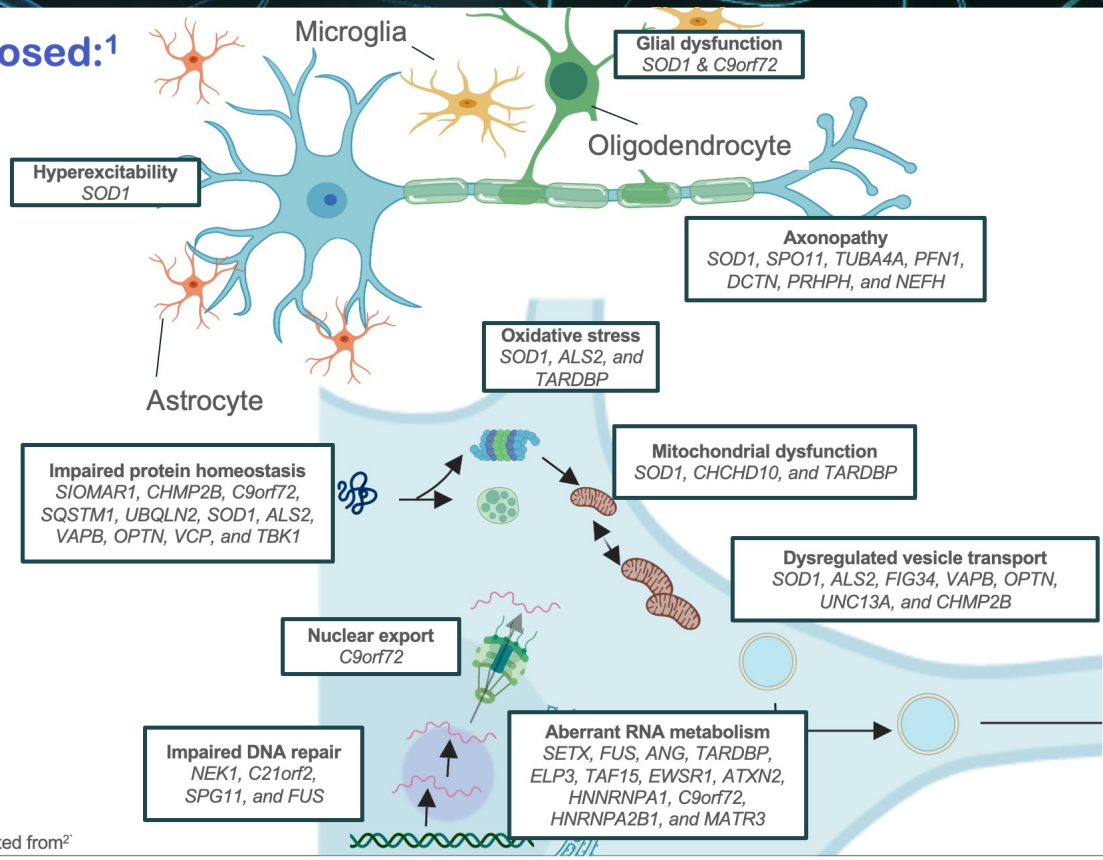
Amyotrophic Lateral Sclerosis (ALS)

Mechanism of disease – The etiology of ALS is not established

A number of mechanisms have been proposed:[1]

- Abnormalities in RNA metabolism
- SOD1-mediated toxicity
- Excitotoxicity
- Cytoskeletal derangements
- Mitochondrial dysfunction
- Viral infections
- Apoptosis
- Growth factor abnormalities
- Inflammatory responses

One disease or a syndrome group with many etiologies?
Pathologic mutations in various unrelated pathways



Adapted from[2]

1. Peters, Ghasemi et al. 2015. **2.** Hardiman, Al-Chalabi et al. 2017.

Amyotrophic Lateral Sclerosis (ALS)

The diagnosis of ALS is suggested when there are **progressive** symptoms, over a period of months to years, consistent with upper and lower **motor neuron dysfunction** that impair **limb**, **bulbar**, **axial**, and **respiratory** function

History and physical examination, supported by electrodiagnostic studies and not excluded by neuroimaging and laboratory studies.

Additional criteria that can aid in diagnosis:

- Frontotemporal executive dysfunction preceding or following the onset of motor symptoms (up to 40% of ALS patients)
- Family history of ALS, other progressive motor disorders

Diagnostic criteria for ALS

Presence of:
- Lower motor neuron signs (including EMG features in clinically unaffected muscles)
- Upper motor neuron signs
- Progression of symptoms and signs

Absence of:
- Sensory signs
- Sphincter disturbances
- Visual disturbances
- Autonomic features
- Basal ganglion dysfunction
- Alzheimer-type dementia
- ALS “mimic” syndromes

Supported by:
- Fasciculation in one or more of the regions
- Neurogenic changes in EMG results
- Normal motor and sensory nerve conduction
- Absence of conduction block

Amyotrophic Lateral Sclerosis (ALS)

Natural history/progression of disease

Initial presentation

Loss of motor neurons results in the primary clinical symptoms and signs of ALS and impairment of limb, bulbar, and axial function.

ALS may manifest in any body segment (bulbar, cervical, thoracic, or lumbosacral), and as upper or lower motor neuron symptoms.

Asymmetric limb weakness is the most common presentation of ALS (80%).

- Upper-extremity onset most often begins with hand weakness
- Lower-extremity onset most often begins with weakness of foot dorsiflexion (foot drop)

Other common early symptoms include:

- Atrophic muscles with hyperreflexia
- Nerve conduction studies (NCS) — Reduced CMAP amplitude in motor NCS, with normal function of sensory nerves
- Progressive worsening of initial signs, such as loss of voice/speech

Upper motor neuron signs	Lower motor neuron signs
• Hyperreflexia • Spasticity • Impaired dexterity • Pathologic reflexes (Babinski, Hoffman) • Muscle weakness	• Flaccidity • Muscle atrophy • Fasciculations • Muscle weakness

Adapted from[1]

Frequently misdiagnosed as:
Stroke
Carpal tunnel syndrome
Lumbar or cervical spine disease

Amyotrophic Lateral Sclerosis (ALS)

Natural history/progression of disease

Disease progression

ALS is relentlessly progressive, with symptoms worsening over time without intervening remissions although there may be plateau phases[1]

Symptoms initially spread within the segment of onset and then to other regions in a relatively predictable pattern[2-4]

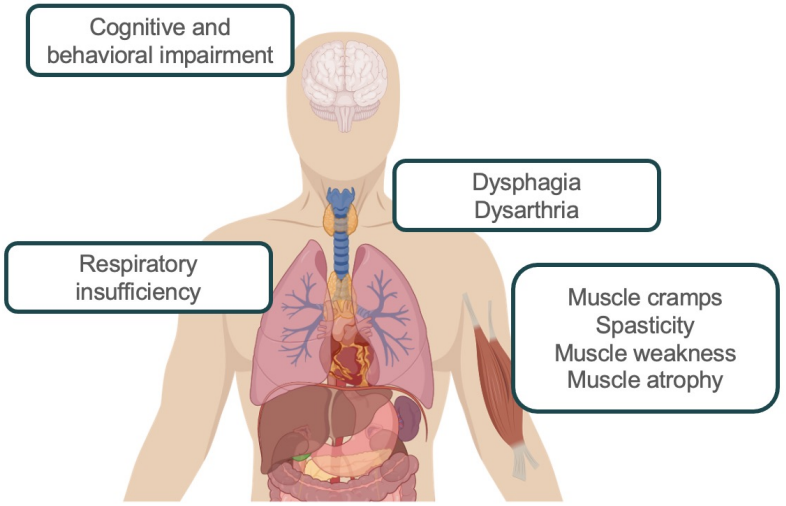
- In patients with unilateral arm onset, the most common (~60-70% of patients) pattern of spread is to the contralateral arm, then to the ipsilateral leg, then to the contralateral remaining leg, and then to the bulbar muscles
- In patients with bulbar onset, the most common pattern of spread is to one arm and then to the contralateral arm

End of life

The progressive course of ALS leads to life-threatening aspects of the disease, neuromuscular respiratory failure and dysphagia.

- Progressive neuromuscular respiratory failure is the most common cause of death in ALS
- Dysphagia poses risk for aspiration of food, liquids, or secretions with resultant pneumonia and may cause malnutrition and dehydration

Clinical manifestations of ALS



Adapted from[4]

1. Bedlack, Vasughan et al. 2016. **2.** Amyotrophic lateral sclerosis and other motor neuron diseases. *Adv Neurol.* 1991. **2.** Ravits, Paul et al. 2007. **3.** Ravits, Laurie et al. 2007. **4.** Hardiman, Al-Chalabi et al. 2017.

Amyotrophic Lateral Sclerosis (ALS)

Mechanism of disease – The etiology of ALS is not established

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One disease or a syndrome group with many etiologies?
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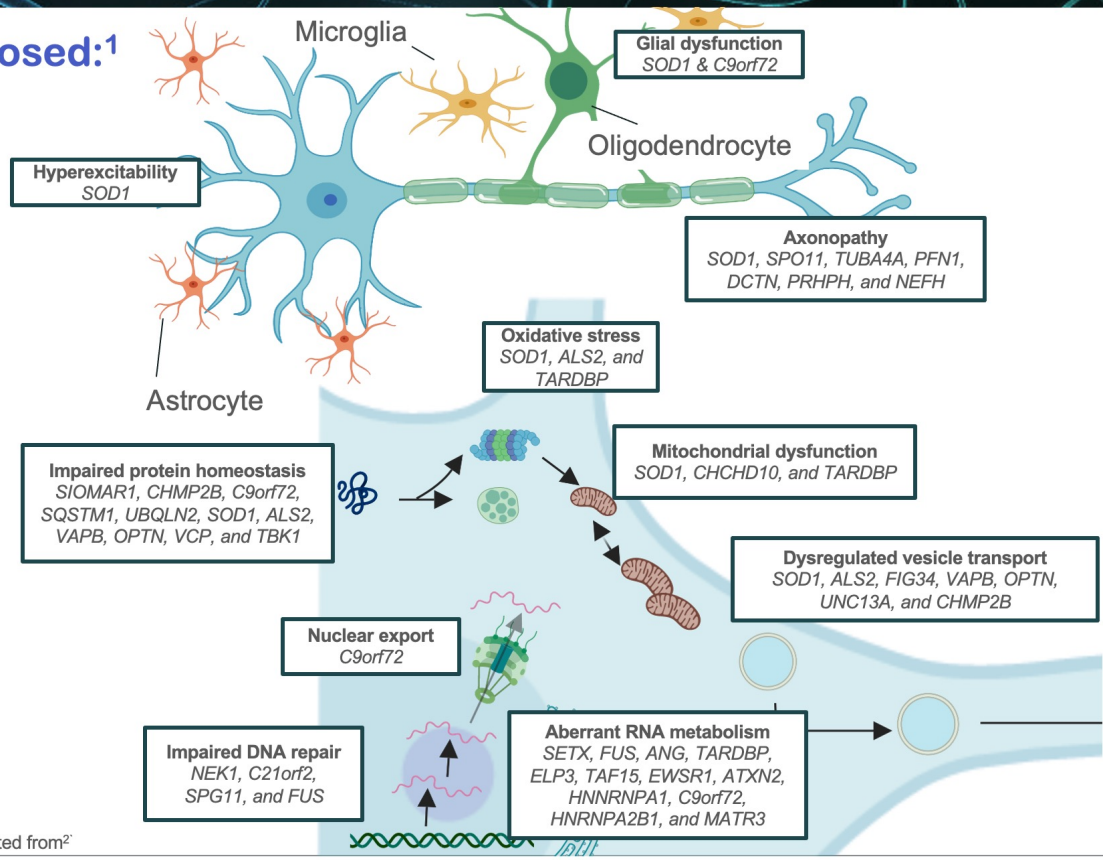
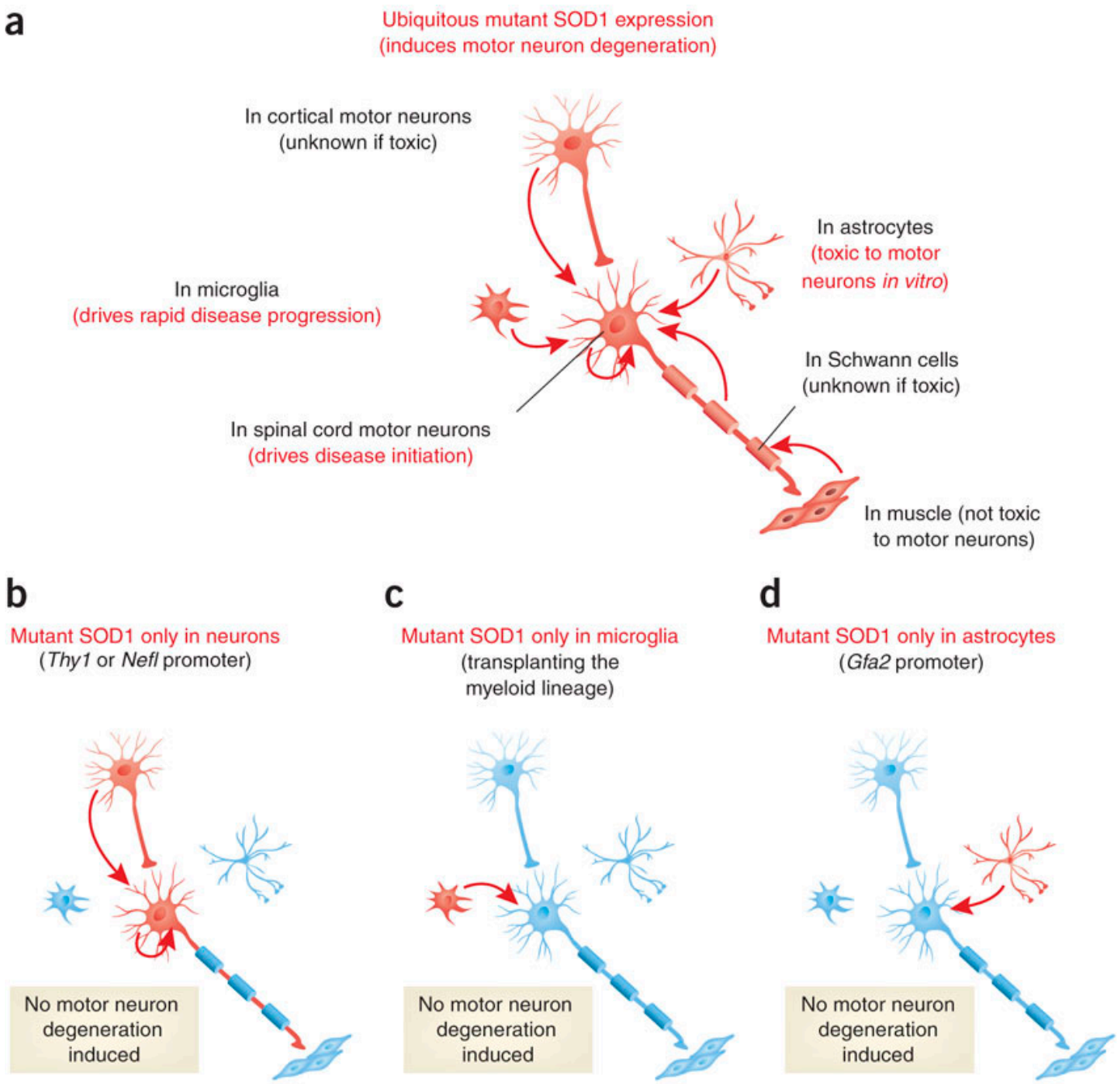


Adapted from[2]

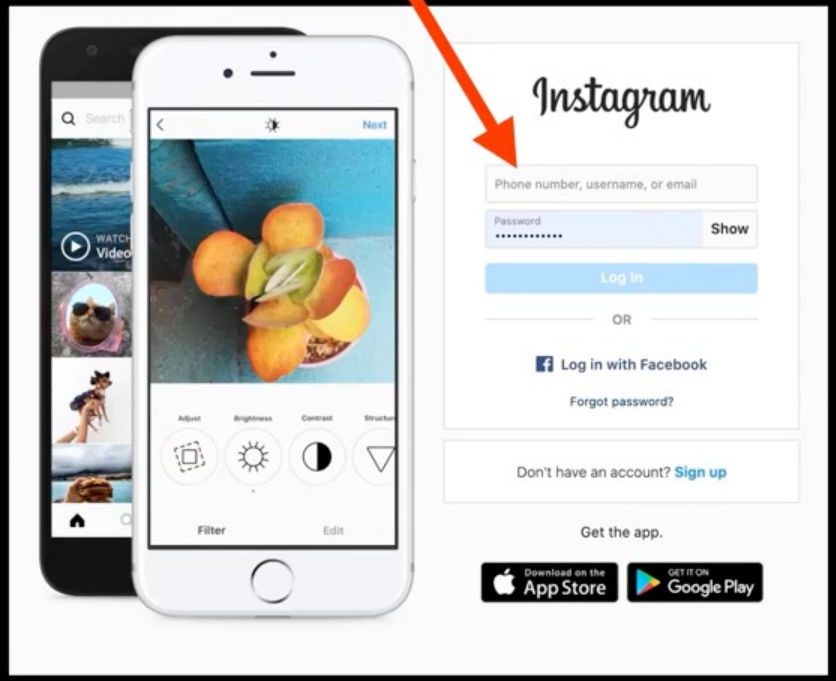
1. Peters, Ghasemi et al. 2015. **2.** Hardiman, Al-Chalabi et al. 2017.

Glia-mediated neurotoxicity in SOD-dependent ALS

- Patients with ALS develop neuroinflammation (astro- and micro-gliosis)
- microglia^{mut} produces ROS (NADPH oxidase)
- astrocytes^{mut} express lower levels of GLT-1
- astrocytes^{mut} express high levels of chromogranin A, which induces release of SOD^{mut} which activates microglia


a
Ubiquitous mutant SOD1 expression
(induces motor neuron degeneration)
In cortical motor neurons
(unknown if toxic)
In astrocytes
(toxic to motor
neurons *in vitro*)
In microglia
(drives rapid disease progression)
In Schwann cells
(unknown if toxic)
In spinal cord motor neurons
(drives disease initiation)
In muscle (not toxic
to motor neurons)
b
Mutant SOD1 only in neurons
(*Thy1* or *Nefl* promoter)
No motor neuron
degeneration
induced
c
Mutant SOD1 only in microglia
(transplanting the
myeloid lineage)
No motor neuron
degeneration
induced
d
Mutant SOD1 only in astrocytes
(*Gfa2* promoter)
No motor neuron
degeneration
induced

#thecatalystuniversity



Spinocerebellar Ataxia (SCA)

PRIMEVIEW

SPINOCEREBELLAR ATAXIA

nature REVIEWS DISEASE PRIMERS

For the Primer, visit doi:10.1038/s41572-019-0074-3

The spinocerebellar ataxias (SCAs) are a group of rare autosomal dominant progressive disorders characterized by loss of balance and coordination, and by slurred speech. As each SCA has a distinct genetic cause, the pathophysiology is heterogeneous.

MECHANISMS

There are >40 genetically distinct SCA subtypes, which are classified either as repeat expansion SCAs or as SCAs that are caused by conventional mutations. One key mechanism underscoring SCAs is polyglutamine (polyQ) repeat expansion. PolyQ repeat expansions cause proteins to have altered conformations, which alters their function, alters their interactions with other proteins, can cause them to oligomerize and can lead to the formation of intranuclear inclusions; these events cause proteotoxicity. SCA-causing proteins without polyQ expansions may also have altered conformations that cause proteotoxicity. Some SCAs are caused by non-protein coding repeat expansions that sequester RNA-binding proteins; other nuclear events that may contribute to the pathogenesis of SCAs are DNA damage, altered chromatin acetylation and changes in transcription. In the cytoplasm, repeat expansions in SCA disease proteins can also cause non-canonical translation, leading to aggregate-prone polypeptides; some SCA-causing mutations directly or indirectly cause ion channel dysfunction, and multiple SCA disease proteins indirectly impair mitochondrial function.

MANAGEMENT

Most SCA-causing mutations result in damage to cerebellar Purkinje neurons; basal ganglia and pontine nuclei in the brainstem may also be involved

Currently no drug that slows or halts SCAs is available

The scale for the assessment and rating of ataxia (SARA) is used to assess ataxia in observational and interventional studies worldwide

EPIDEMIOLOGY

Determining the prevalence of SCAs is challenging owing to the limited number of population-based epidemiological studies and the high number of SCA-causing genes. PolyQ SCAs are the most frequent; of these, SCA3 (also known as Machado-Joseph disease) is the most common SCA worldwide (20–50% of families with a dominant ataxia), followed by SCA2 (13–18% of families with SCA) and SCA6 (13–15% of families with SCA). Founder effects explain the presence of high-frequency rare Mendelian diseases in some populations. As the genetic defect is unidentified in 30–48% of patients with SCA, new causative genes will likely be discovered.

DIAGNOSIS

For most patients with SCA, the onset of ataxia occurs in the third or fourth decade of life and is equated with the time the patient first noticed unsteadiness of gait. However, symptoms likely begin several years before manifest ataxia in a pre-ataxia stage. Other symptoms include the loss of fine motor skills, speech and swallowing problems, oculomotor abnormalities and non-ataxia symptoms. If there is clinical evidence for a diagnosis of SCA, molecular genetic testing is initiated. A targeted genetic test is recommended if a known SCA genotype is in the family, if the phenotype is suggestive of a specific SCA or if a SCA is prevalent in the population. Otherwise, and also when targeted tests are negative, a step-by-step approach to diagnosis, starting with tests for mutations that cause polyQ SCAs, is recommended.

OUTLOOK

Progress in the development of therapies for SCAs is limited; riluzole, valproic acid, varenicline and lithium carbonate gave encouraging results in clinical studies, but no clear evidence of benefit was established. Our increasing understanding of the mechanisms underlying SCAs should help to identify targets for symptom-modifying and disease-modifying therapies, as well as biomarkers for assessing disease progression and treatment efficacy. Treatment in the pre-ataxia stage, before irreversible brain degeneration occurs, is desirable. Finally, the decreasing cost of genetic tests (including whole-exome sequencing), and the availability of new tests (such as long-read whole-genome sequencing), should aid the diagnosis of SCAs and further inform epidemiology.

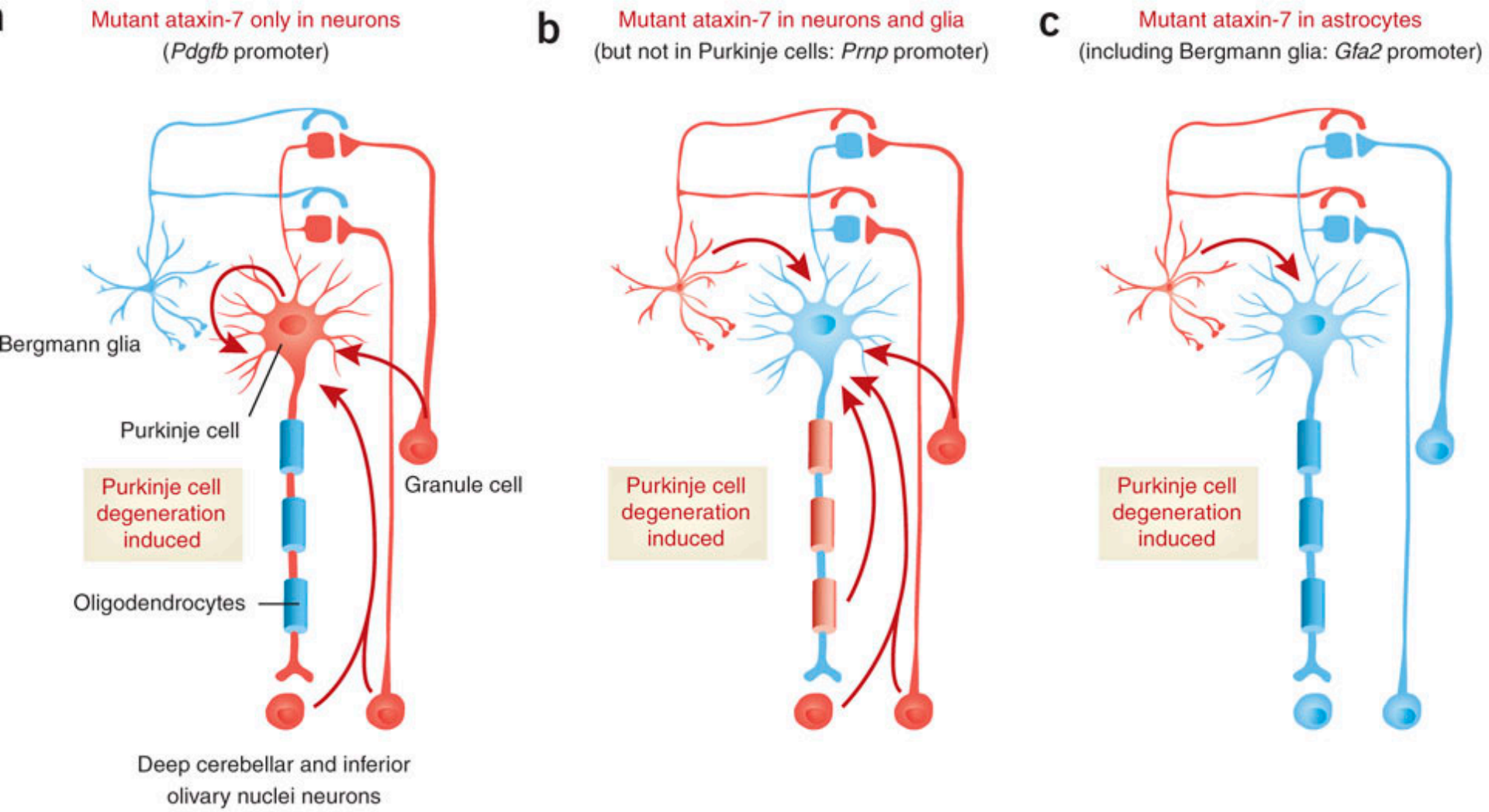
doi:10.1038/s41572-019-0081-4; Article citation ID: (2019) 5:25

Written by Katharine H. Wrighton; designed by Laura Marshall

Glial neurotoxicity in SCA7

- polyQ expansion in the antaxin7 gene

- Bergmann glia expresses less GLAST


Mutant ataxin-7 only in neurons
(*Pdgfb* promoter)
Bergmann glia
Purkinje cell
Granule cell
Purkinje cell degeneration induced
Oligodendrocytes
Deep cerebellar and inferior olivary nuclei neurons
b
Mutant ataxin-7 in neurons and glia
(but not in Purkinje cells: *Prnp* promoter)
Purkinje cell degeneration induced
c
Mutant ataxin-7 in astrocytes
(including Bergmann glia: *Gfa2* promoter)
Purkinje cell degeneration induced

Hungtinton Disease

Glial
in Hungtinton Disease

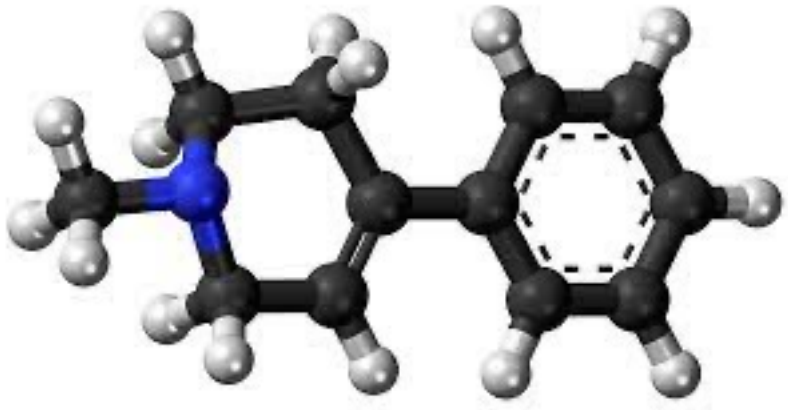
- Indirect evidence of microglial involvement using minocycline

- Mutated protein Huntingtin (HTT) accumulates in the nucleus of the astrocytic cells, reducing the expression of GLT-1

Parkinson’s Disease

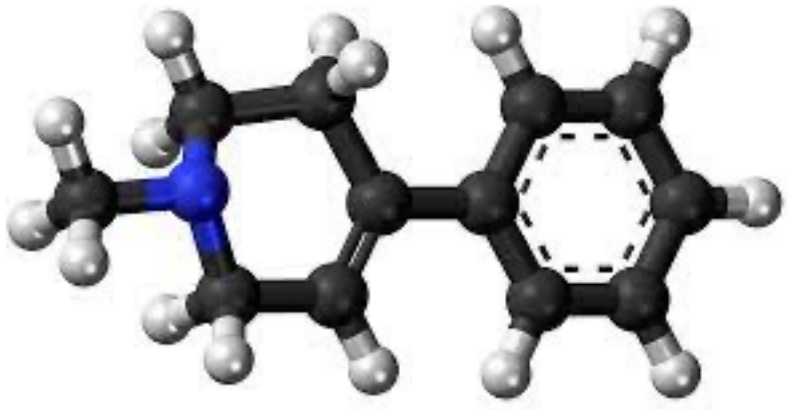
Parkinson’s Disease

MPTP-induced parkinsonism: an historical case series



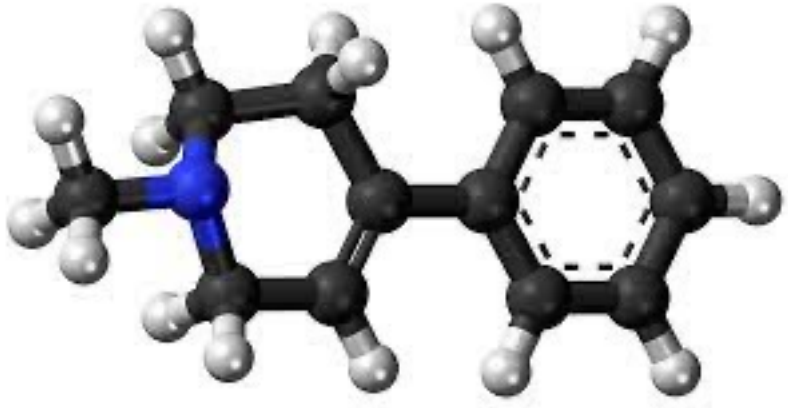
In 1982, seven young adults developed severe and irreversible parkinsonism shortly after they injected themselves with a new synthetic heroin.1 Sample analyses revealed that this synthetic heroin consisted of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),2 a potent neurotoxin targeting neurons within the substantia nigra.

MPTP-induced parkinsonism: an historical case series



MPTP isn't actually a drug, it's an impurity in a drug. It happens if you cook a synthetic heroin analog called 1-methyl-4-phenyl-4-propionoxypiperidine at too high a temperature. Reactions are too fast and you end up with MPTP contaminating the drug.

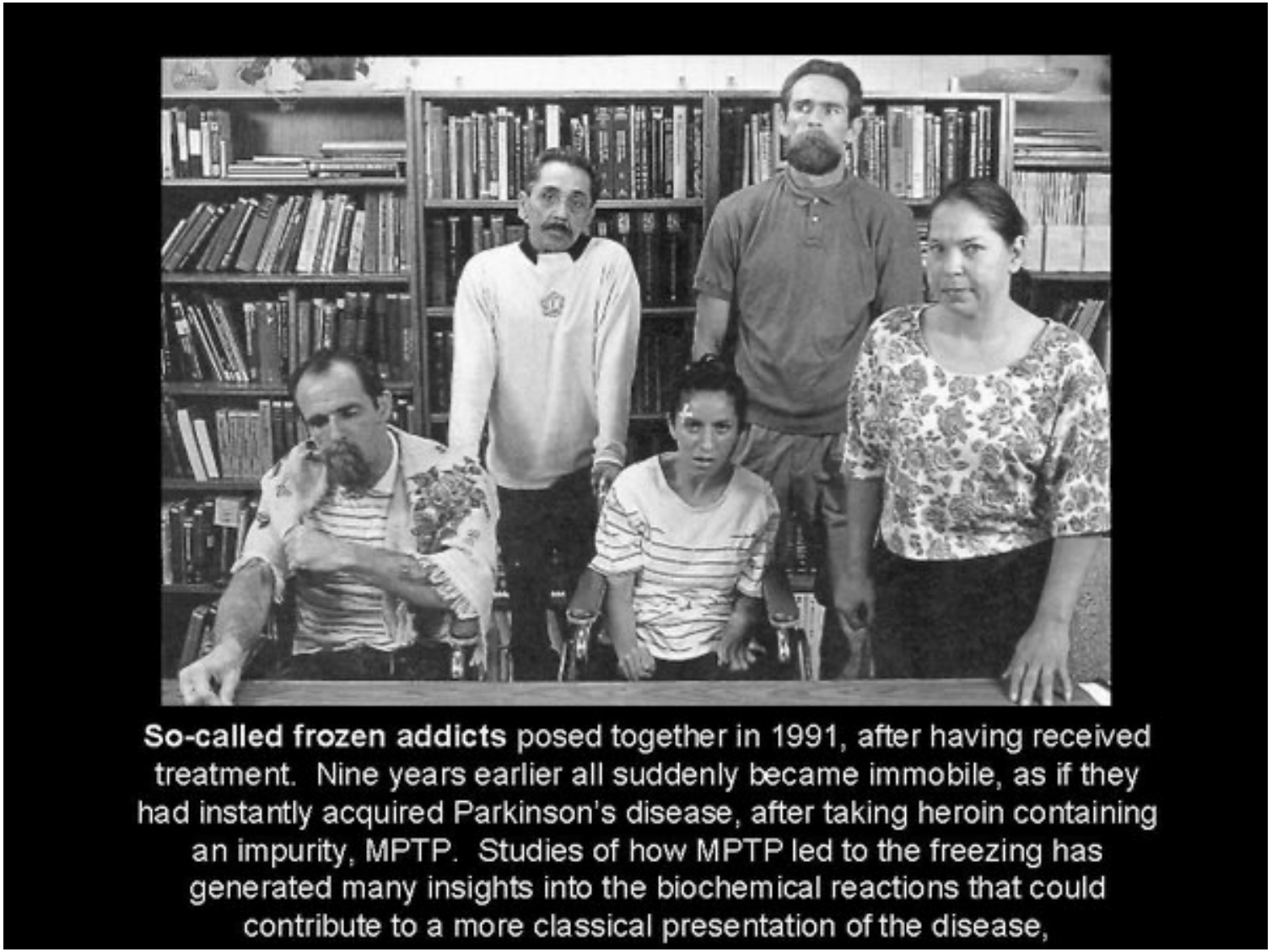
MPTP-induced parkinsonism: an historical case series



MPTP is catabolized by monoamine oxidase-B in the brain into 1-methyl-4-phenylpyridinium, which is a potent neurotoxin that selectively and efficiently destroys dopaminergic neurons in the voluntary motor control area of the brain. The result is rapid and irreversible onset of Parkinson's.

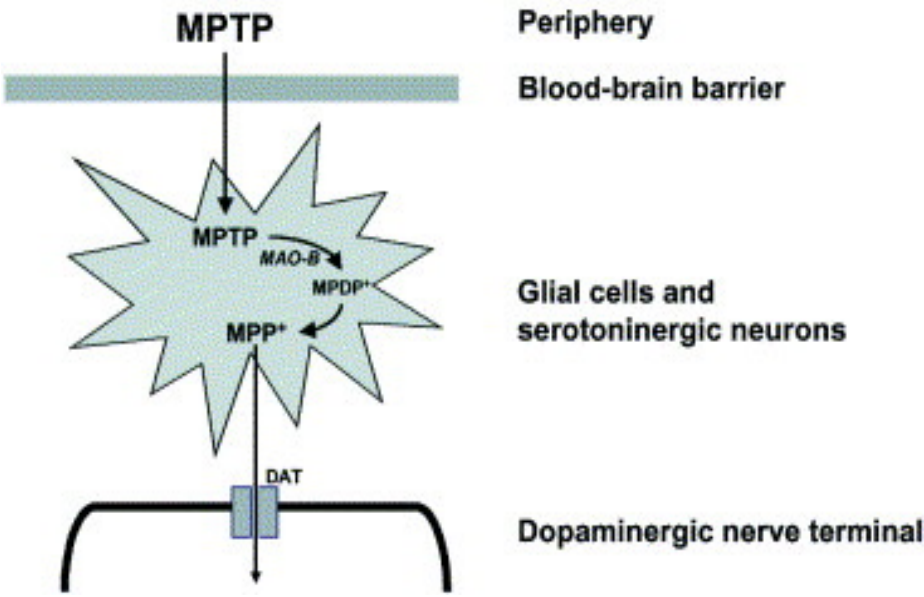
It didn't cause Parkinson's later in life, it caused Parkinson's later that week.

MPTP-induced parkinsonism: an historical case series



So-called frozen addicts posed together in 1991, after having received treatment. Nine years earlier all suddenly became immobile, as if they had instantly acquired Parkinson's disease, after taking heroin containing an impurity, MPTP. Studies of how MPTP led to the freezing has generated many insights into the biochemical reactions that could contribute to a more classical presentation of the disease,

MPTP-induced parkinsonism: the role of astrocytes



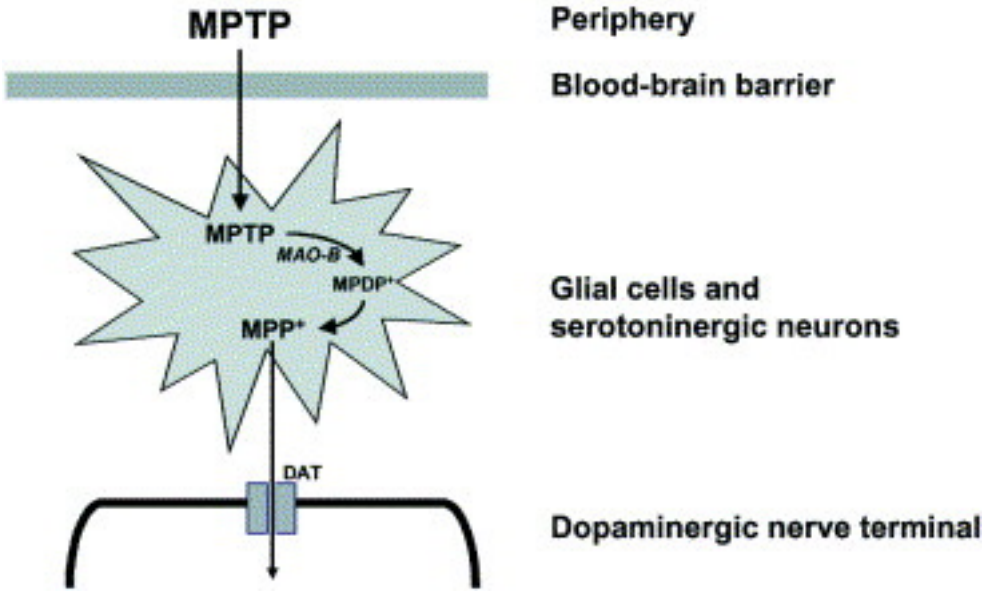
PD-associated motor deficits are characterized by nigrostriatal dopaminergic-neuron loss.

The parkinsonian protoxicant MPTP is activated in the central nervous system (CNS) by astrocytic monoamine oxidase-B to form the active toxicant 1-methyl-4-phenylpyridinium (MPP^+).

Membrane-impermeable MPP^+ is taken up by neurotransmitter transporters into catecholaminergic neurons.

Inside cells, MPP^+ inhibits mitochondrial complex I, reducing mitochondrial ATP output and favoring ROS formation.

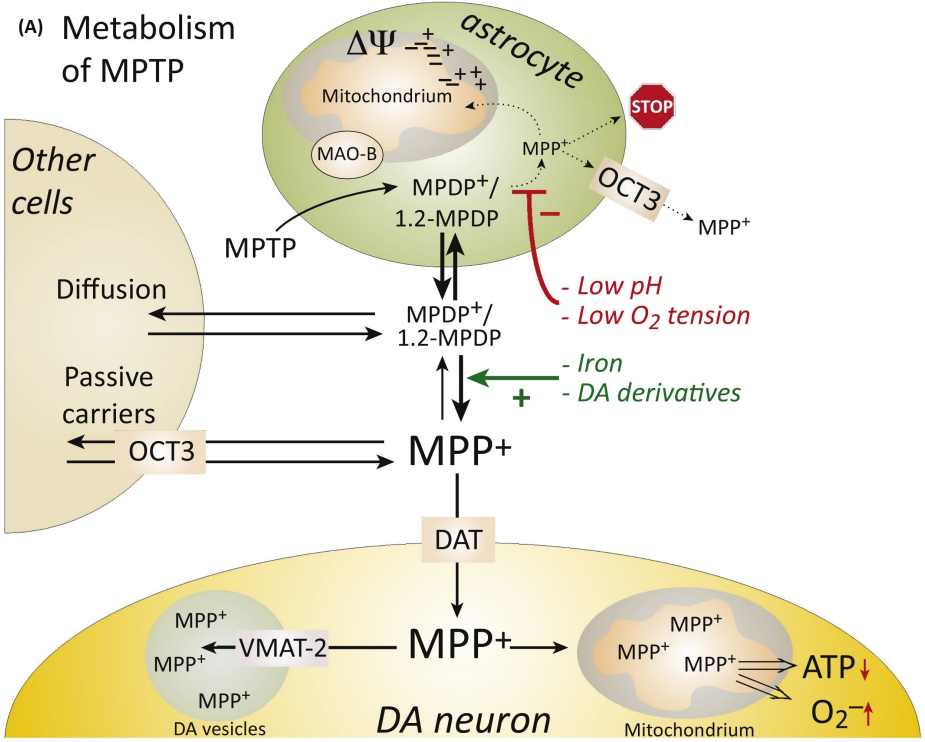
MPTP-induced parkinsonism

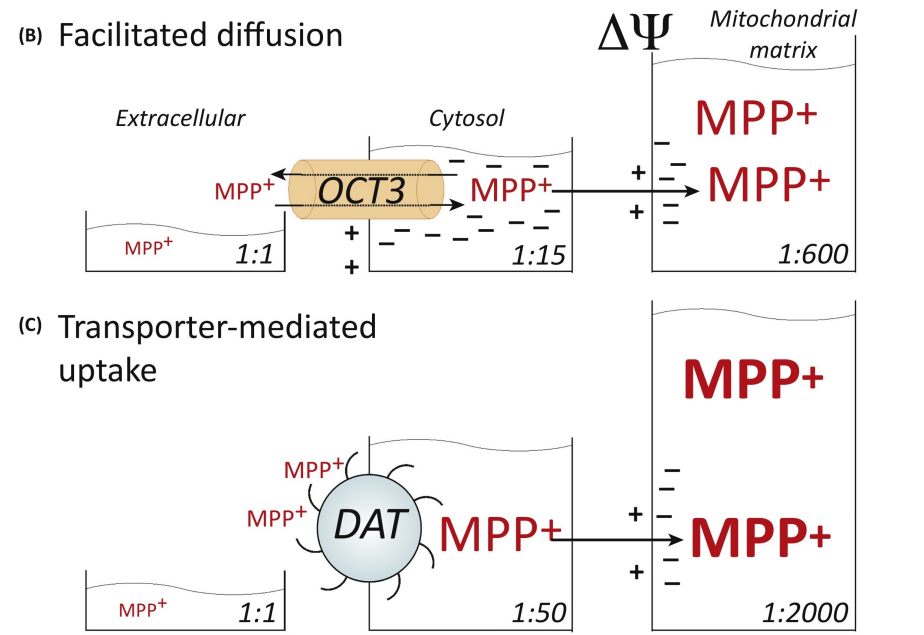


In MPTP-exposed brains, different catecholaminergic populations show large sensitivity differences, with a distinct nigrostriatal dopaminergic-neuron degeneration, reflecting the degeneration pattern in PD.

Intrinsic factors, such as MPP^+ uptake and/or vesicular-sequestration kinetics, neuronal morphology, and intracellular Ca^{2+} handling, distinguish sensitive from resistant neuronal subpopulations in the MPTP model and in PD.

The neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a Parkinson's disease (PD)-like syndrome by inducing degeneration of nigrostriatal dopaminergic neurons. Studies of the MPTP model have revealed the pathomechanisms underlying dopaminergic neurodegeneration and facilitated the development of drug treatments for PD.

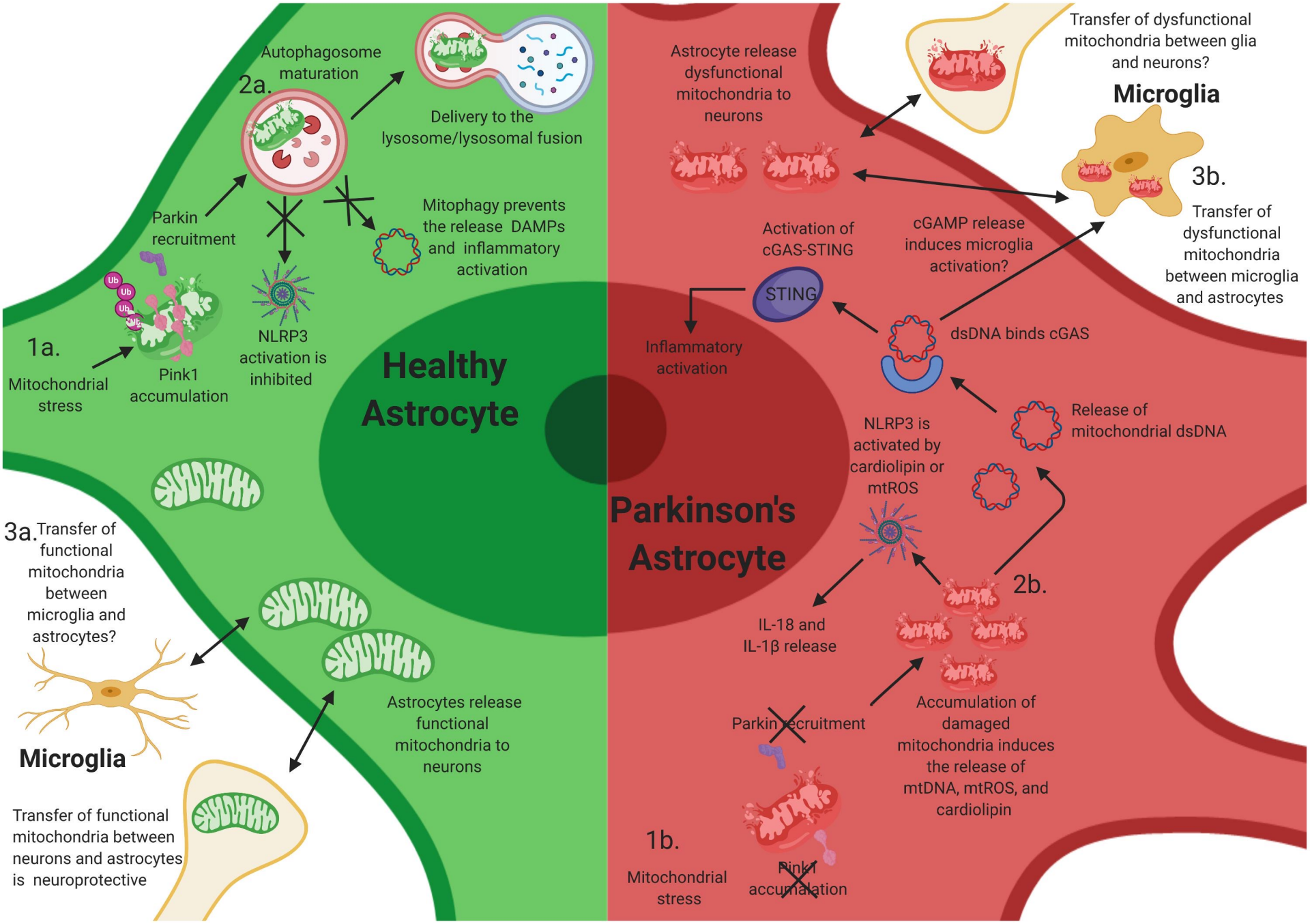

(A) Metabolism of MPTP
astrocyte
ΔΨ
Mitochondrium
MAO-B
STOP
MPP+
OCT3
MPP+
MPDP+/ 1.2-MPDP
MPTP
Other cells
Diffusion
- Low pH
- Low O2 tension
MPDP+/ 1.2-MPDP
- Iron
- DA derivatives
Passive carriers
OCT3
MPP+
DAT
MPP+
MPP+
MPP+
VMAT-2
MPP+
MPP+
MPP+
MPP+
MPP+
ATP
O2−
DA vesicles
DA neuron
Mitochondrium


(B) Facilitated diffusion
ΔΨ
Mitochondrial matrix
Extracellular
Cytosol
MPP+
MPP+
OCT3
MPP+
MPP+
MPP+
1:1
1:15
1:600
(C) Transporter-mediated uptake
MPP+
MPP+
MPP+
DAT
MPP+
MPP+
MPP+
1:1
1:50
1:2000

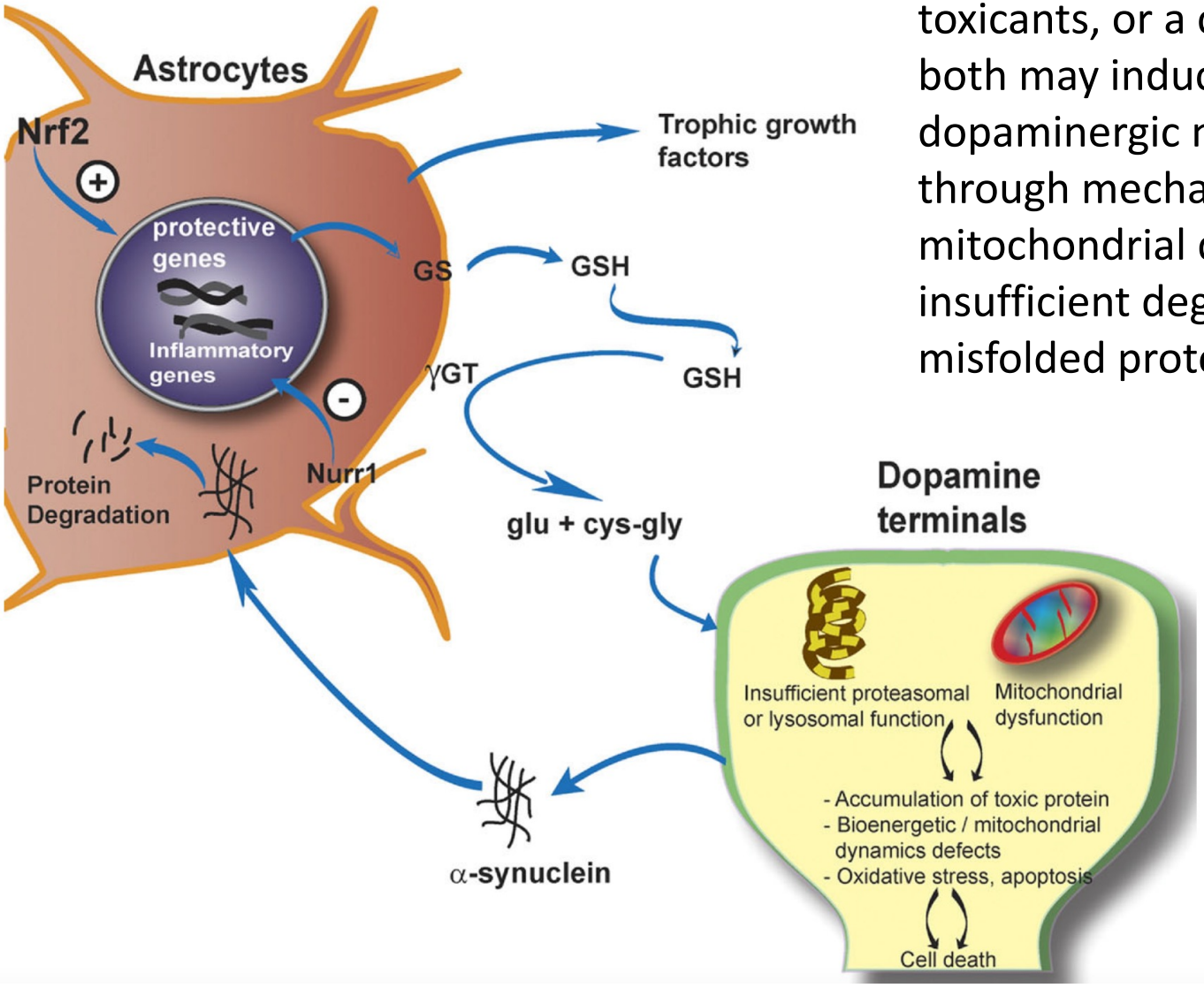
Glial neurotoxicity in PD

- The MPTP toxicity is due to its conversion to MPP+ by monoamine oxidase B. MPP+ is uptaken by neurons expressing specific transporters

- Microglia determines neurotoxicity producing NO

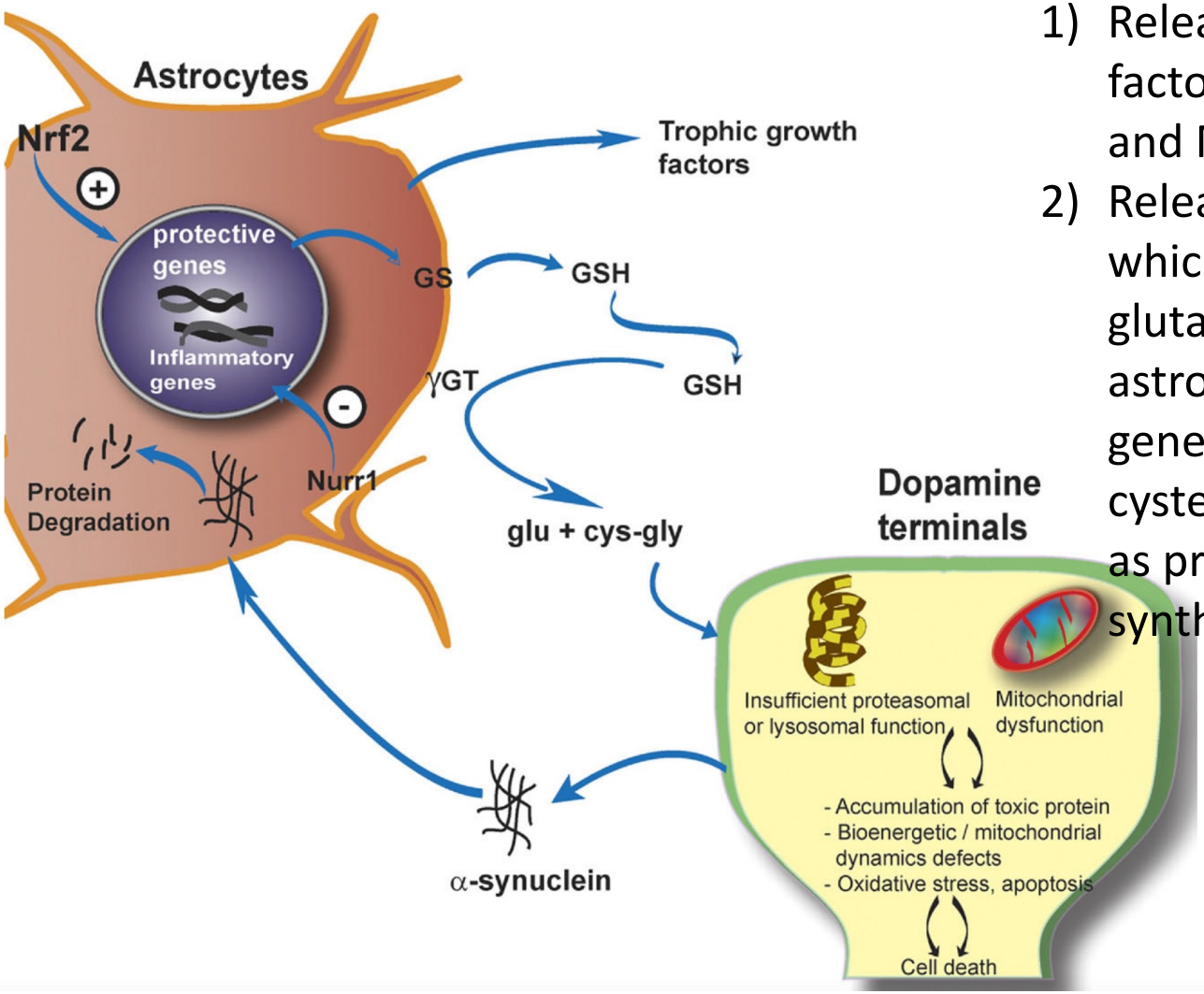

Autophagosome maturation
2a.
Delivery to the lysosome/lysosomal fusion
Parkin recruitment
Mitophagy prevents the release DAMPs and inflammatory activation
NLRP3 activation is inhibited
1a.
Mitochondrial stress
Pink1 accumulation
Healthy Astrocyte
3a. Transfer of functional mitochondria between microglia and astrocytes?
Microglia
Astrocytes release functional mitochondria to neurons
Transfer of functional mitochondria between neurons and astrocytes is neuroprotective
Astrocyte release dysfunctional mitochondria to neurons
Transfer of dysfunctional mitochondria between glia and neurons?
Microglia
3b.
Transfer of dysfunctional mitochondria between microglia and astrocytes
Activation of cGAS-STING
cGAMP release induces microglia activation?
STING
Inflammatory activation
dsDNA binds cGAS
Release of mitochondrial dsDNA
NLRP3 is activated by cardiolipin or mtROS
Parkinson's Astrocyte
2b.
IL-18 and IL-1β release
Parkin recruitment
Accumulation of damaged mitochondria induces the release of mtDNA, mtROS, and cardiolipin
1b.
Mitochondrial stress
Pink1 accumulation

Potential neuroprotective pathways of astrocytes in PD



Genetic mutations, environmental toxicants, or a combination of both may induce nigral dopaminergic neurotoxicity through mechanisms such as mitochondrial dysfunction and insufficient degradation of misfolded proteins.

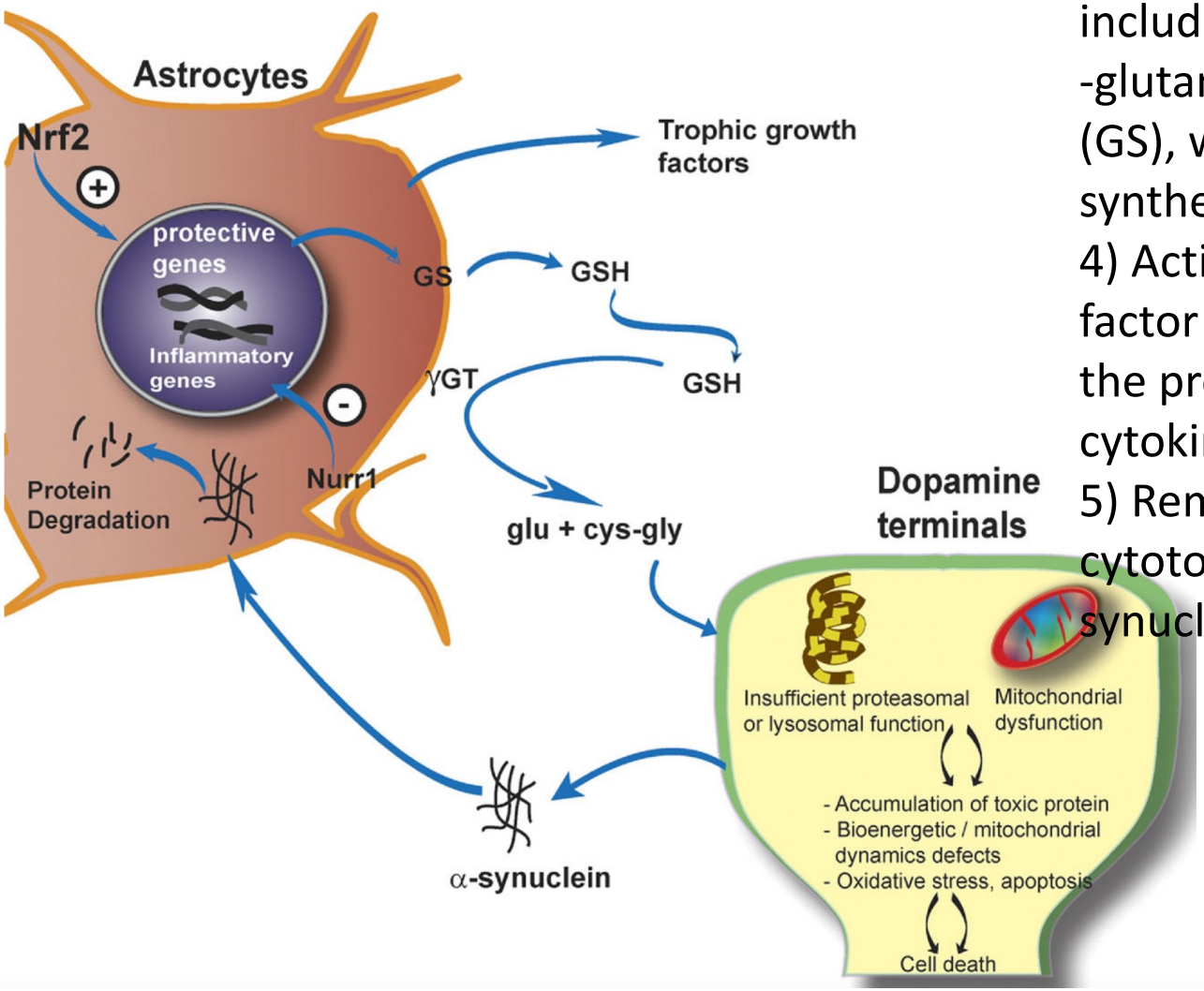
Potential neuroprotective pathways of astrocytes in PD



Astrocytes may mediate neuroprotection through the following pathways.

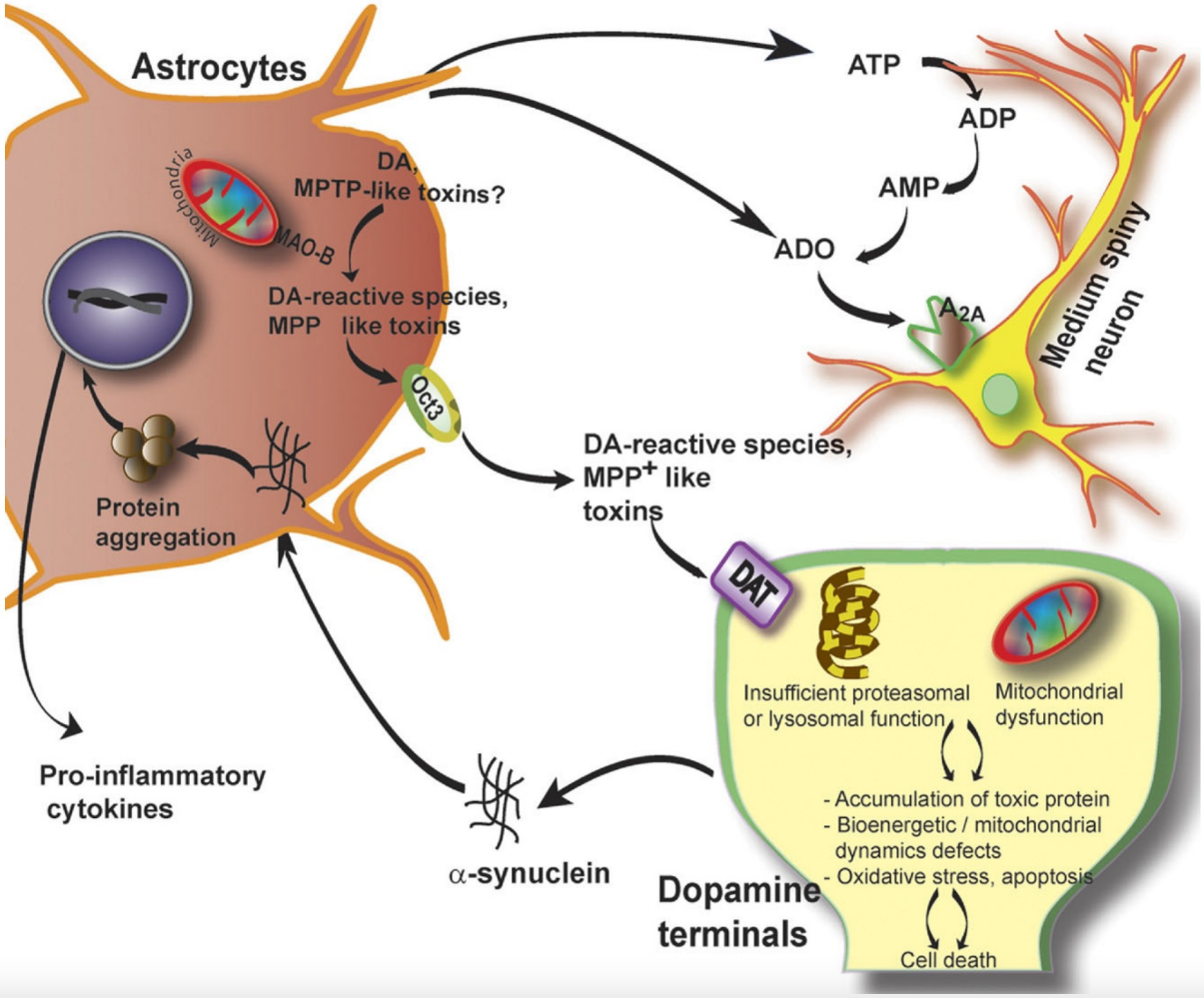
1) Release of trophic growth factors, such as bFGF, GDNF, and MANF).
2) Release of glutathione (GSH), which is then cleaved by -glutamyltranspeptidase on astrocytic plasma membrane to generate glutamate and cysteinylglycine, which serves as precursors for neuronal GSH synthesis

Potential neuroprotective pathways of astrocytes in PD



3) Activation of the transcription factor Nrf2 leads to expression of genes containing the antioxidant response element (ARE), including
-glutamylcysteine synthetase (GS), which is involved in GSH synthesis.
4) Activation of the transcription factor Nurr1, which suppresses the production of inflammatory cytokines.
5) Removal and degradation of cytotoxic molecules, such as -synuclein.

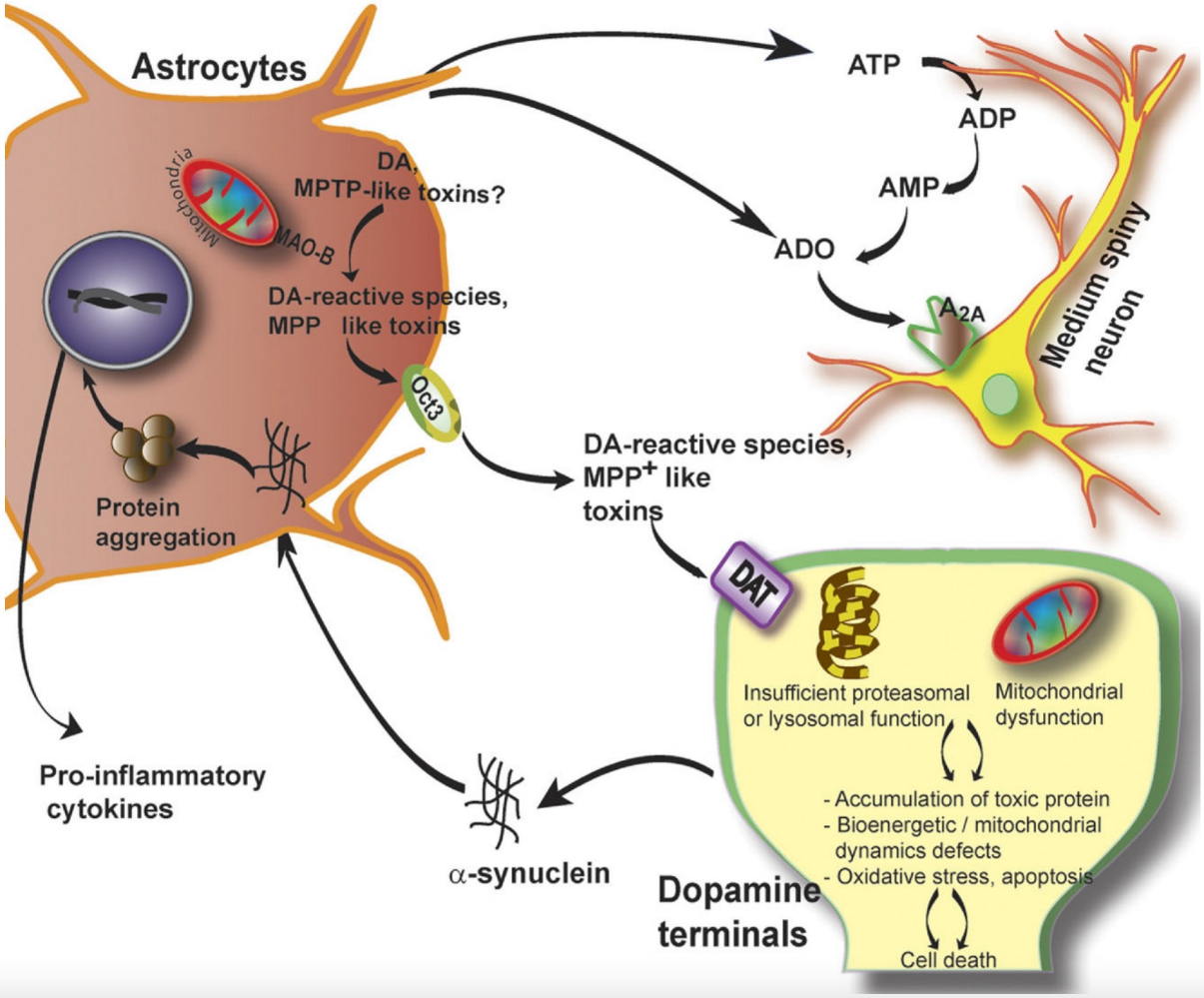
Potential neurotoxic pathways of astrocytes in PD.



Astrocytes may also adversely affect the survival and function of dopaminergic neurons through the following mechanisms:

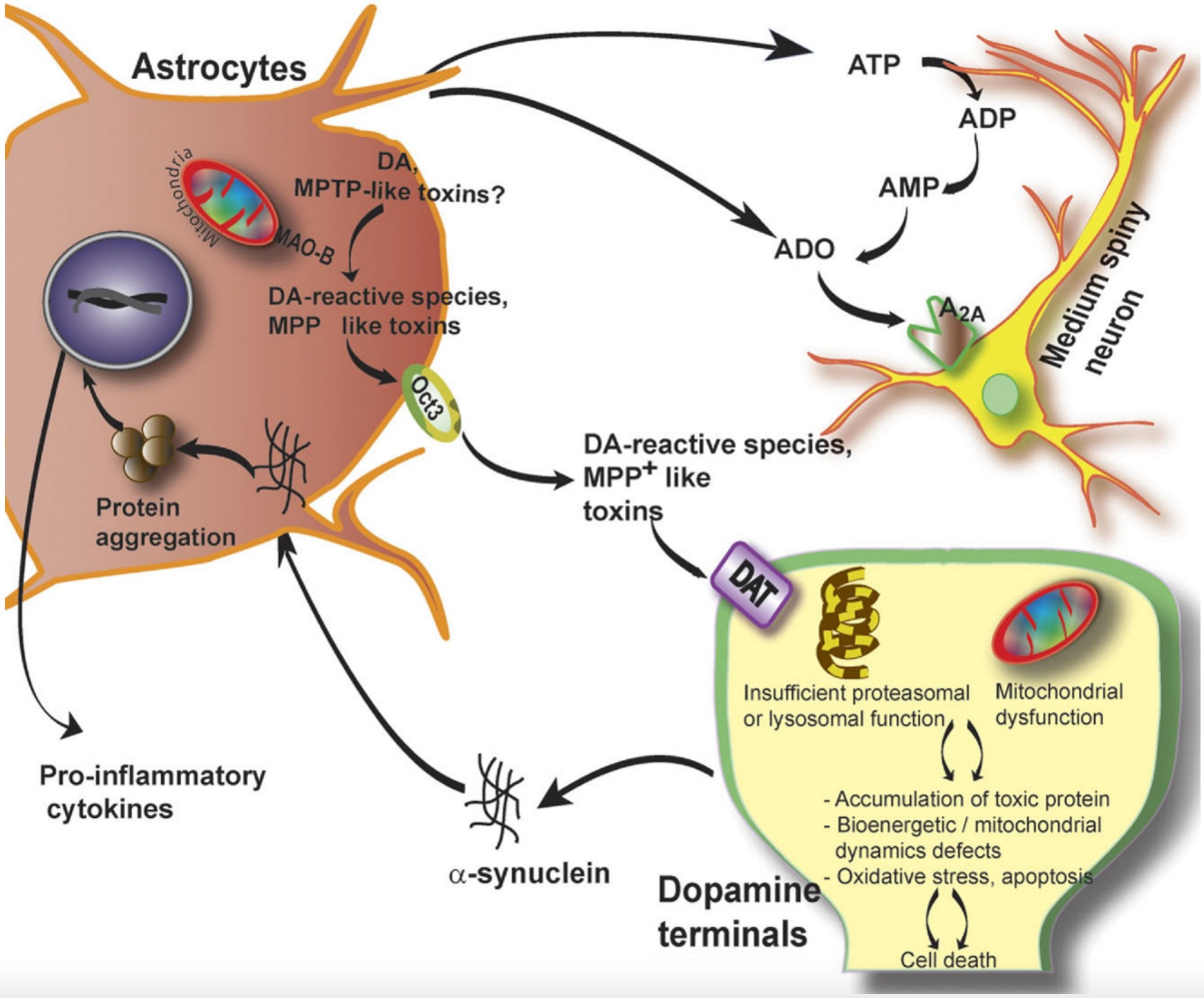
1) Release of proinflammatory cytokines under pathological conditions such as accumu- lation of aggregated alpha-synuclein

Potential neurotoxic pathways of astrocytes in PD.



2) Monoamine oxidase-B (MAO-B) mediated release of cytotoxic molecules such as dopamine-related oxidants and MPP□-like organic cations through the organic cation transporter (Oct3) into the extracellular space where they are subsequently transported into DA neurons through the dopamine transporter (DAT).

Potential neurotoxic pathways of astrocytes in PD.



3) Astrocytes can also release adenosine (ADO) directly or indirectly via ATP. ADO may increase movement disorders in patients with PD through the A2A receptors in striatal medium spiny neurons.

Cerebral ischemia

- GLOBAL: astrocytes are relatively resistant to ischemia and become activated

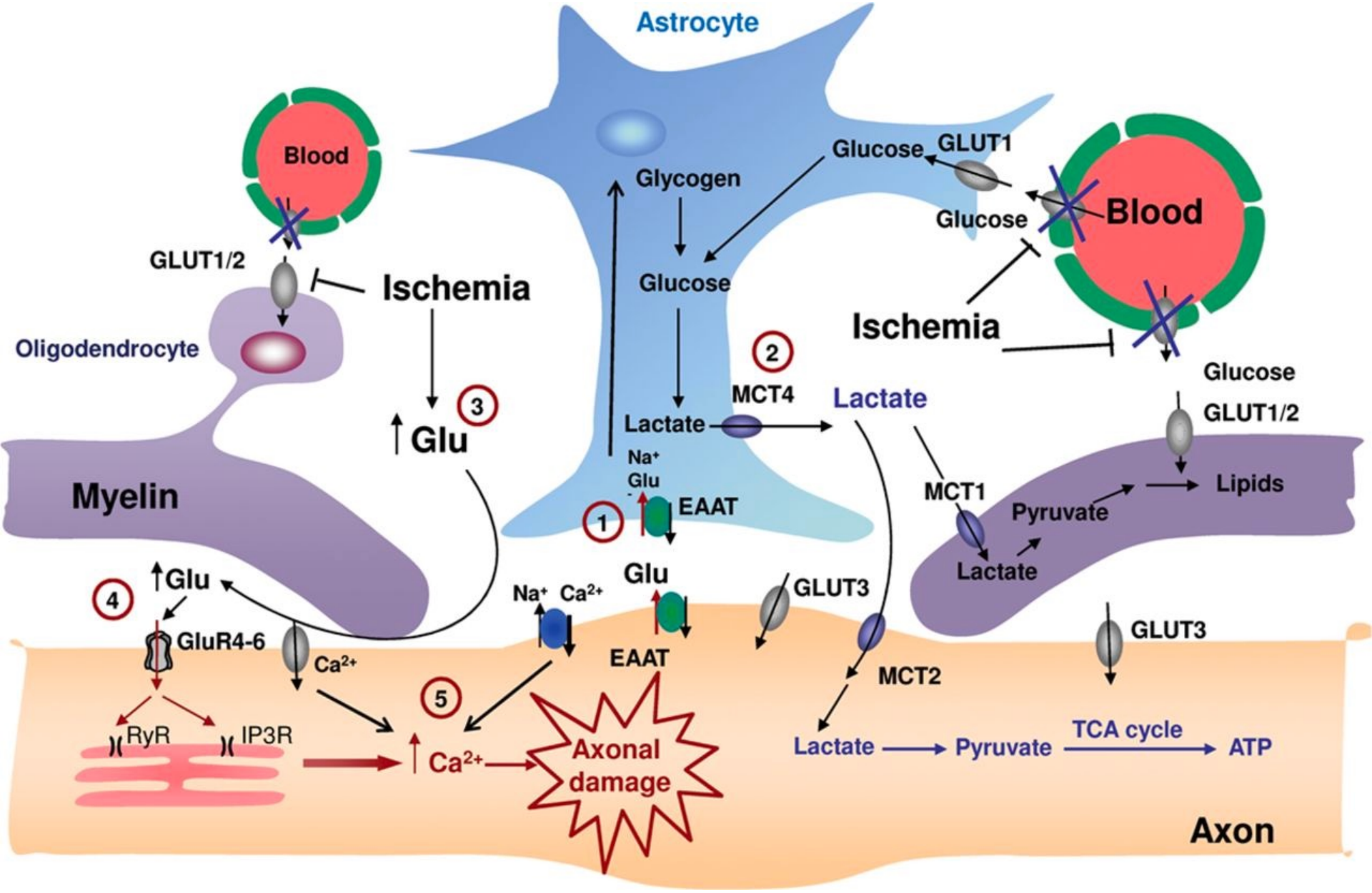
- FOCAL: in the "core" area the astrocytes also die, in the "penumbra" it happens more slowly and following the acidification of the LEC and formation of the ROS

Ischemic stroke

Astrocytic alterations

Ischemia

- the reduction of ATP production causes the cell to depolarize with reversal of Glu transport
- the increase in $[Ca^{2+}]_i$ can induce vesicular fusion
- acidosis and the reduction of $[Ca^{2+}]_e$ can promote the exit of Glu through emi-channels
- ATP released by dead cells actives P2X7 which induces the release of Glu
- cerebral edema activates volume-sensitive channels that allow Glu to pass


Astrocyte
Blood
GLUT1/2
Ischemia
Oligodendrocyte
Myelin
Glycogen
Glucose
GLUT1
Glucose
Blood
Ischemia
Glucose
GLUT1/2
Lipids
Pyruvate
MCT1
Lactate
2
MCT4
Lactate
3
Glu
Lactate
Na+
Glu
EAAT
1
4
Glu
GluR4-6
Ca2+
Na+ Ca2+
Glu
EAAT
GLUT3
GLUT3
MCT2
5
RyR
IP3R
Ca2+
Axonal damage
Lactate
Pyruvate
TCA cycle
ATP
Axon

Astrocytic role in Cerebral Ischemia

- propagate the "dead zone" from the core to the penumbra through Ca2 + waves and the "spreading depression" waves
- the latter are induced at a frequency (1 every 15 min) are induced by the high [K +] in the area around the core and are related to cell death in the ischemic zone

Three mechanisms: 1 lactic acidosis

- Astrocytes have important glycogen stores: lactic acidosis prevails during ischemia

- The lowering of the pH induces an activation of the Na + / H + exchanger and the Na + input leads to the Na + / Ca2 + transport inversion with Ca2 + overload in the astrocytes

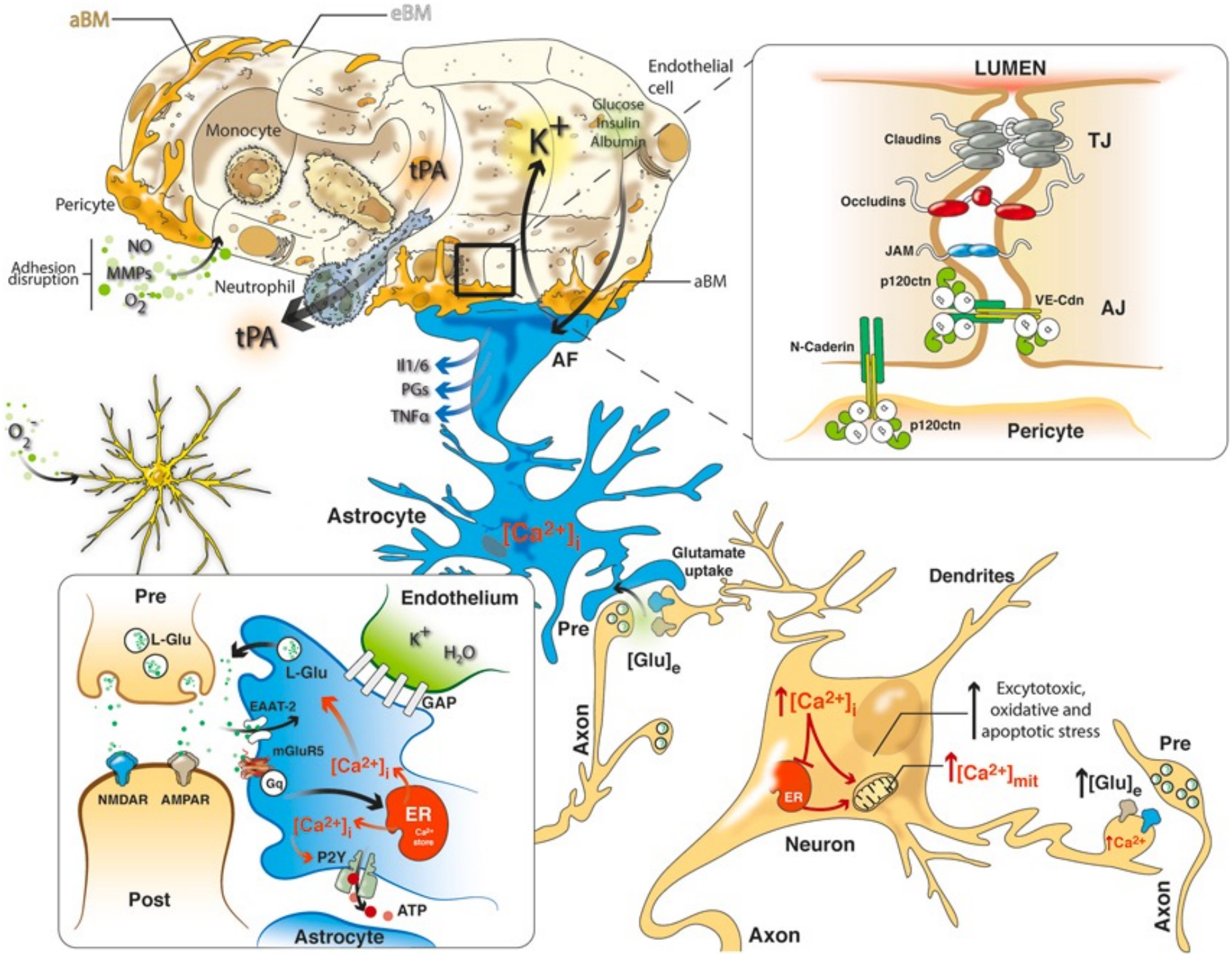
Three mechanisms: 2 Glutamate release

- The increase of Ca2 + in astrocytes induces release of ATP and Glu. ATP stimulates P2Y and generates waves of Ca2 +, P2X and increases the release of Glu to which they are permeable (as well as Ca2 +) [ATP adenosine]
- Glu vesicular release
- The reduction of the value of Vm (-20mV) causes an inversion of the Glu transporters that pump it outside the cell
- Astrocytic swelling activates volume-activated channels (VRAC) that are permeable to anions
- Vesicular release of d-ser following Ca2 + increases induced by AMPAR activation

Three mechanisms: 3 modulation of gap junctions and hemanal

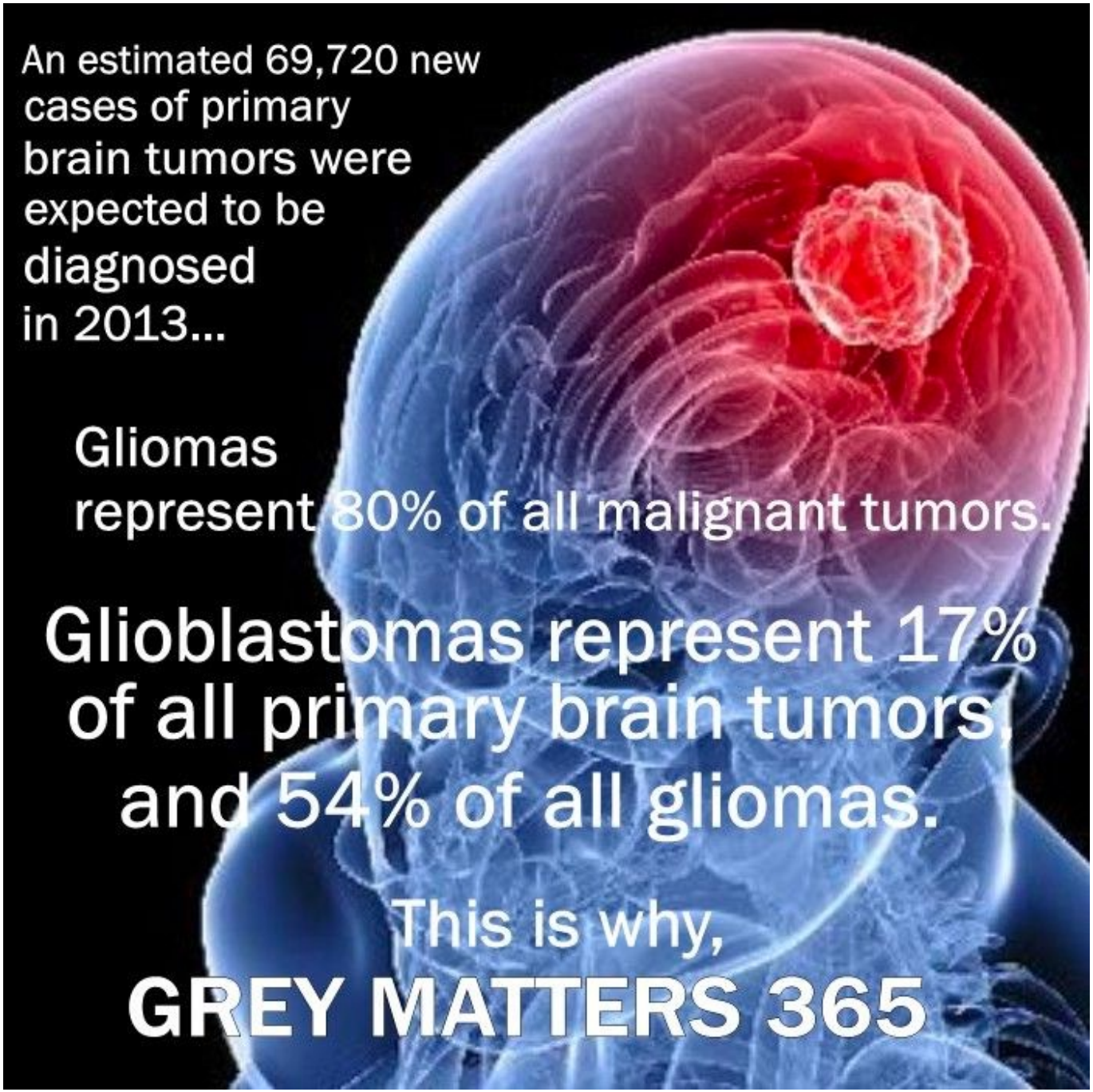
- The gap junctions are closed (partially)

- The emichals open (pass Glu, glutathione)


aBM
eBM
Endothelial cell
Monocyte
Pericyte
Glucose
Insulin
Albumin
K+
tPA
NO
MMPs
O2
Adhesion disruption
Neutrophil
tPA
aBM
AF
Il1/6
PGs
TNFα
O2-
Astrocyte
[Ca2+]i
LUMEN
Claudins
TJ
Occludins
JAM
p120ctn
VE-Cdn
AJ
N-Caderin
p120ctn
Pericyte
Glutamate uptake
Dendrites
Pre
[Glu]e
Axon
Pre
Endothelium
L-Glu
L-Glu
K+
H2O
GAP
EAAT-2
mGluR5
Gq
[Ca2+]i
NMDAR
AMPAR
ER
Ca2+ store
[Ca2+]i
P2Y
Post
ATP
Astrocyte
↑[Ca2+]i
Excytotoxic, oxidative and apoptotic stress
↑[Ca2+]mit
ER
Neuron
↑[Glu]e
↑Ca2+
Pre
Axon
Axon

Neurotoxic action of glia in glioma

- Glioma cells express a Glu-cystine exchanger which increases the$[Glu]_e$
- The infiltrating microglia produces TGF-β which promotes tumor growth

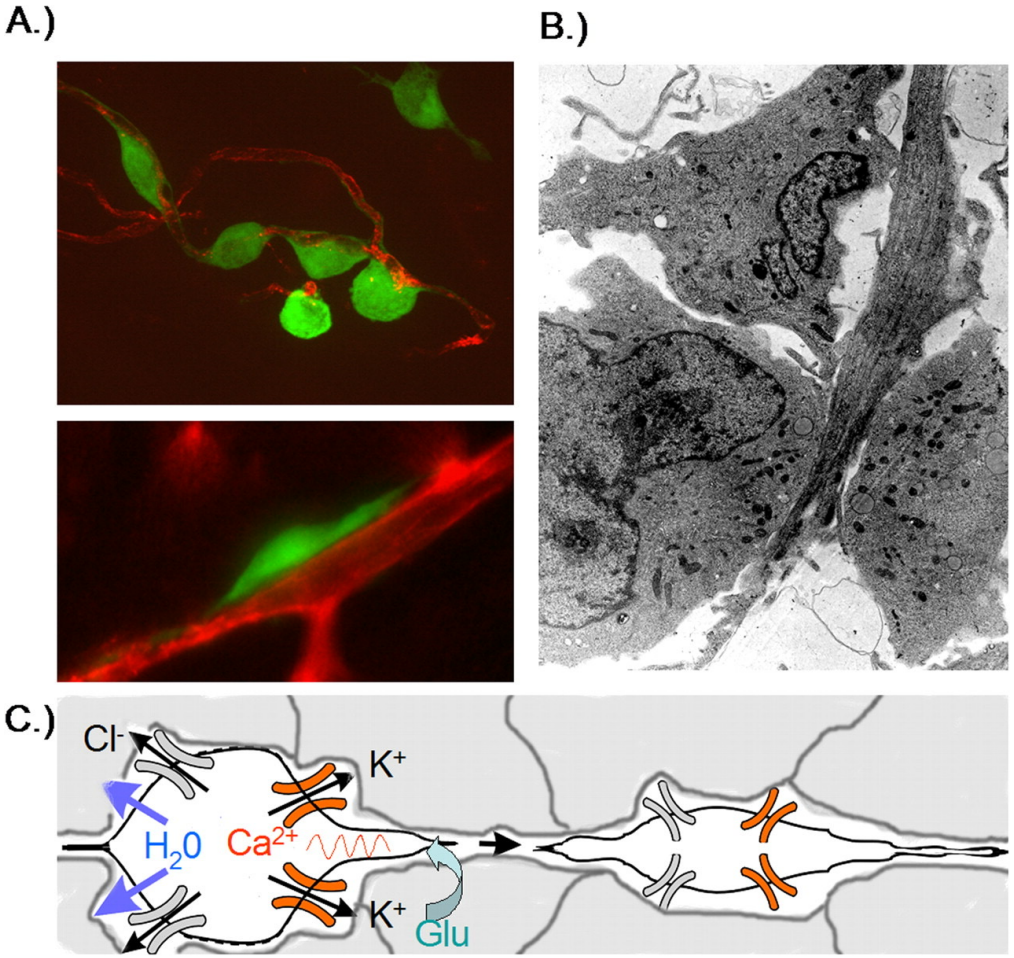

An estimated 69,720 new cases of primary brain tumors were expected to be diagnosed in 2013...
Gliomas represent 80% of all malignant tumors.
Glioblastomas represent 17% of all primary brain tumors, and 54% of all gliomas.
This is why,
GREY MATTERS 365

glioblastoma multiforme (WHO, IV grade)

- grows in a space confined by cranium
- does not disseminate through blood stream
- diffuse invasiveness into brain parenchyma

- migrate into the CNS along nerve fibers and blood vessels

glioma migration and ion channels

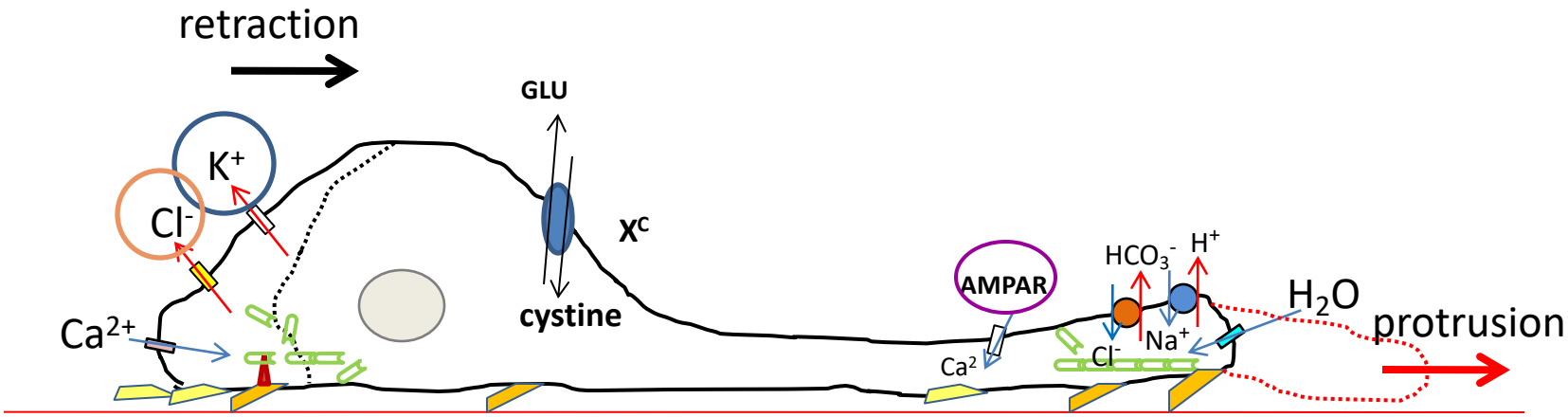


Sontheimer, 2008

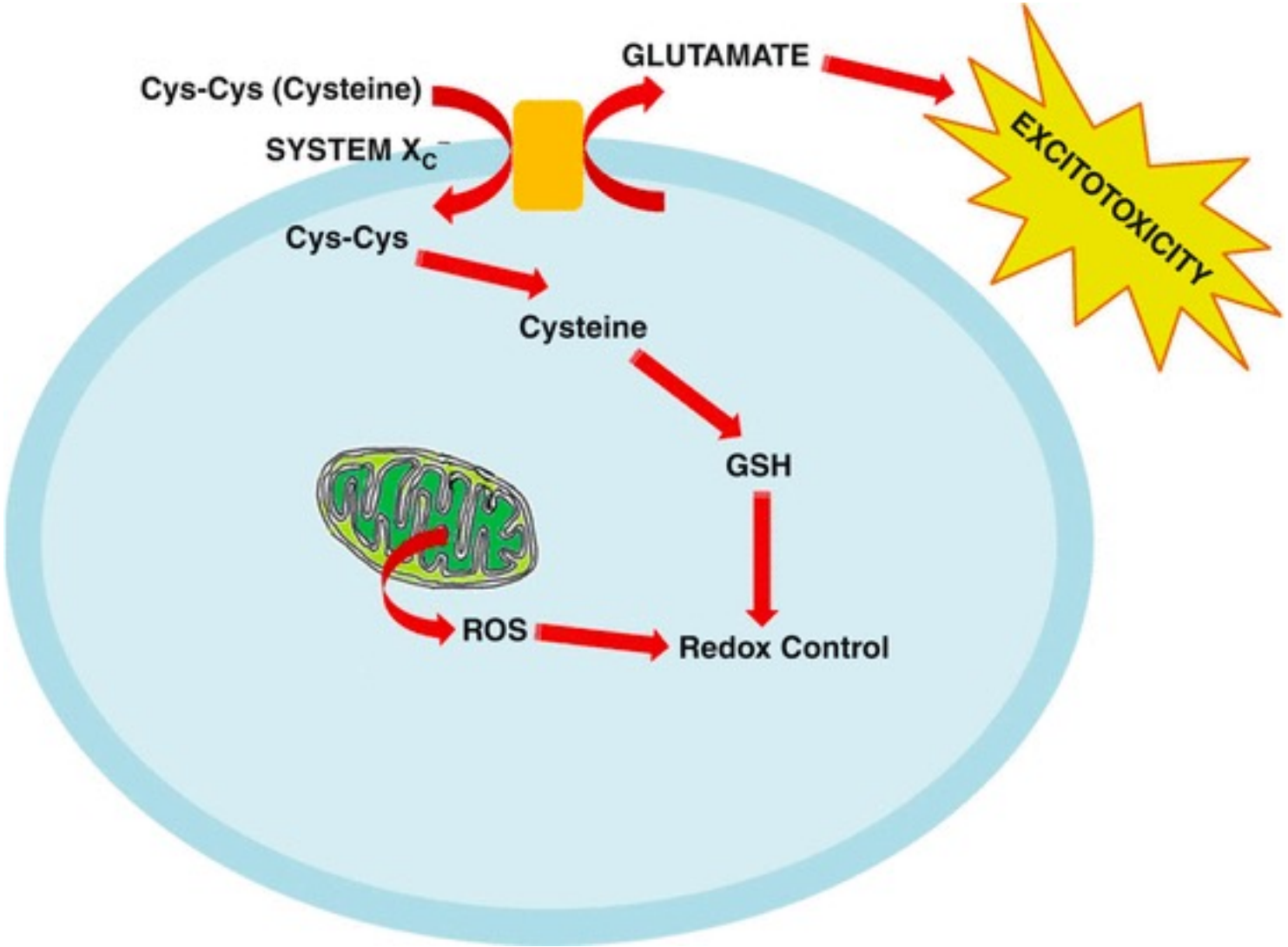
Ion channels involved in glioma migration

- K^+ channels (Ca^{2+} activated: BK, IK)
- Cl^- channels (voltage-activated: ClC2, ClC-3)
- Ca^{2+}-permeable AMPA receptors

Ion channels involved in glioma migration



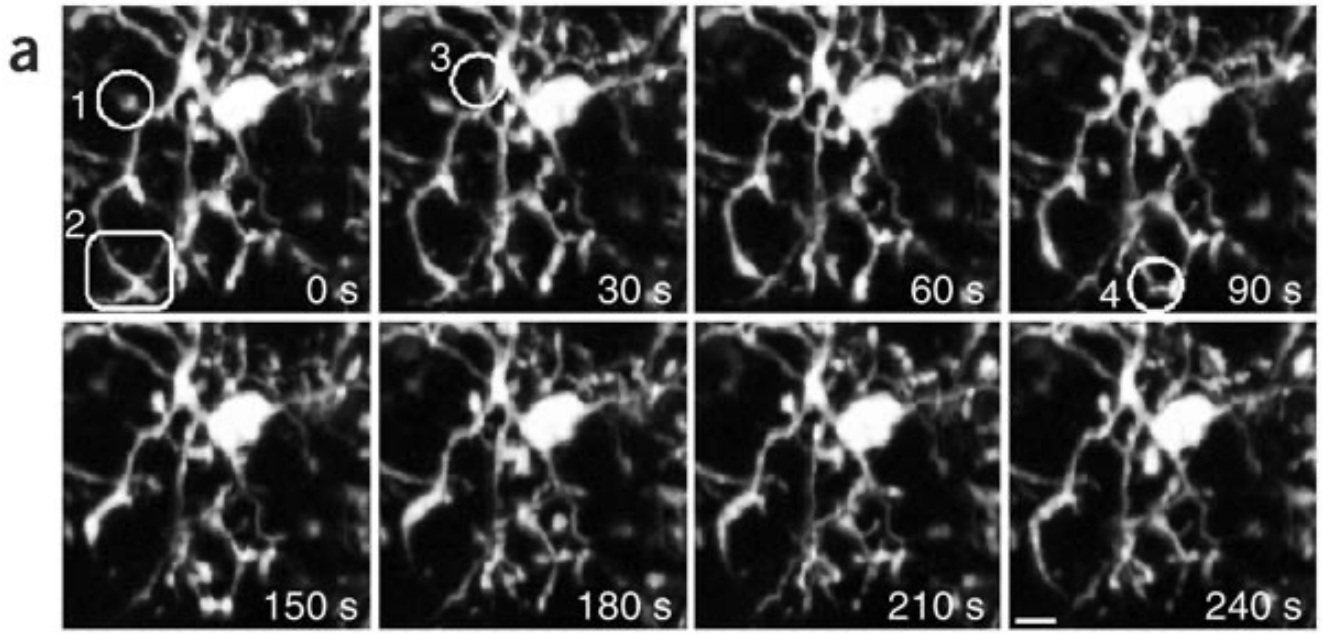
Glioma glutamate release

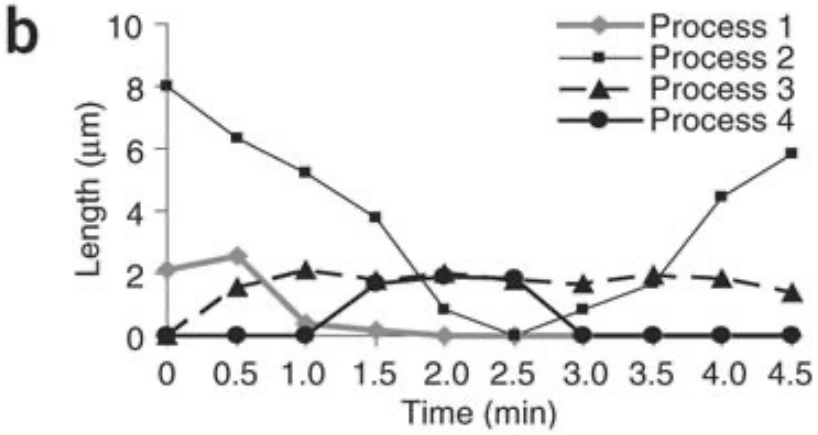


Neuroprotective action of the glia

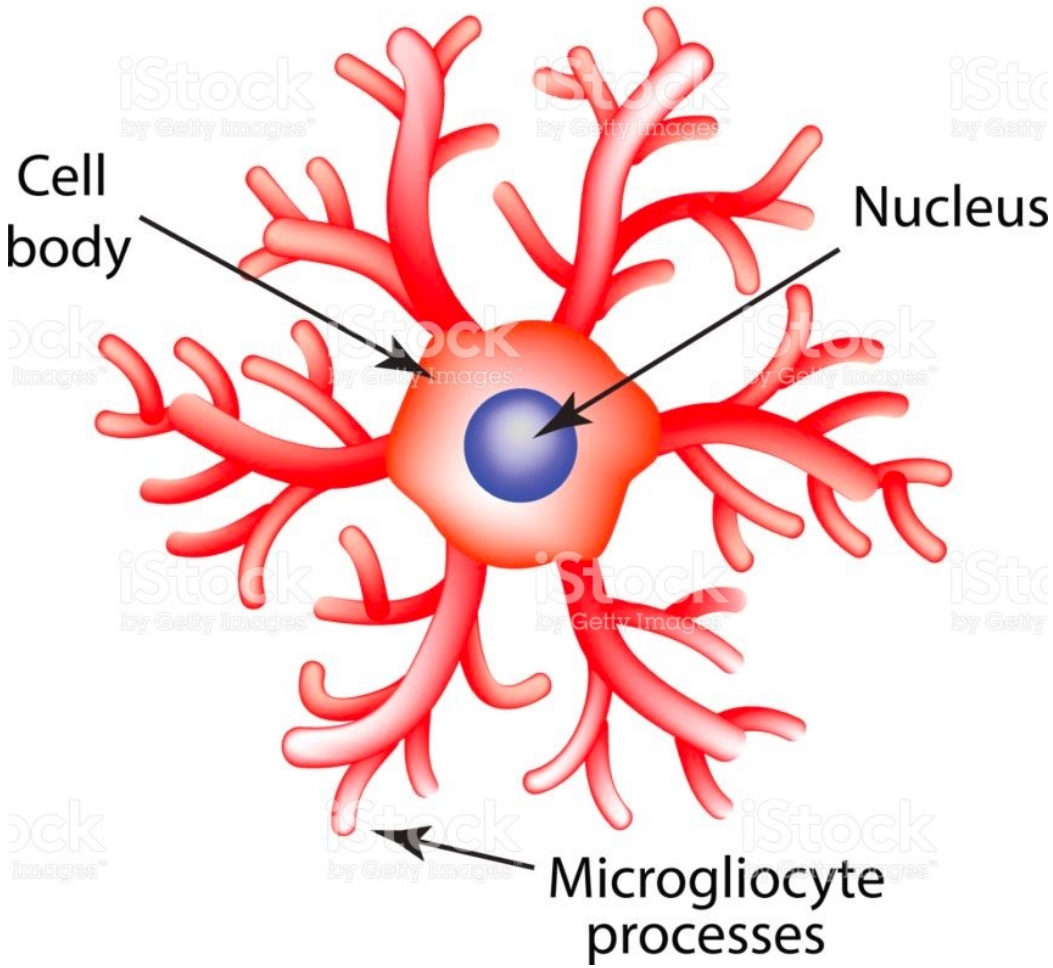
The good and bad of glial activation

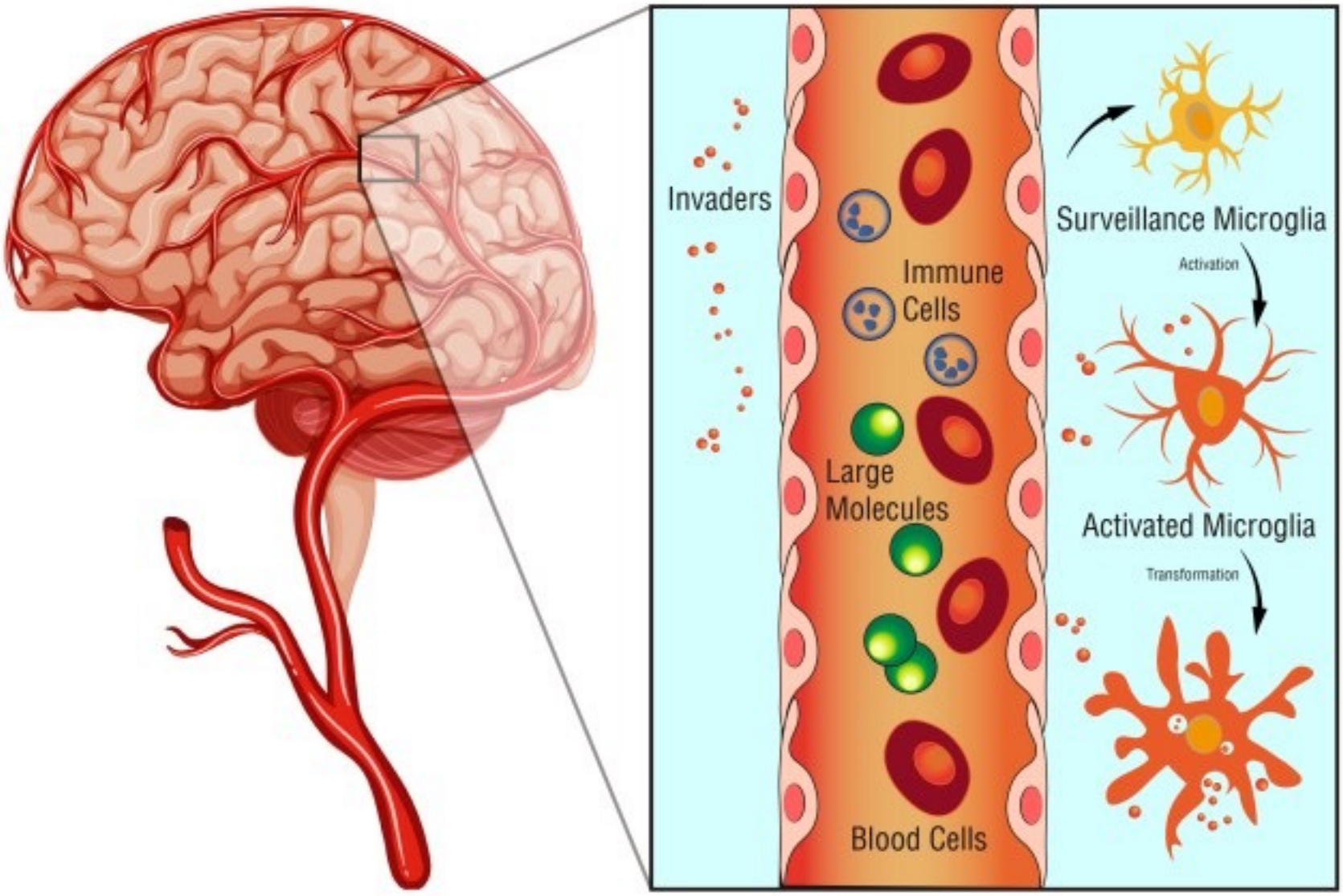
The microglia "resting" is continuously in activity with its processes



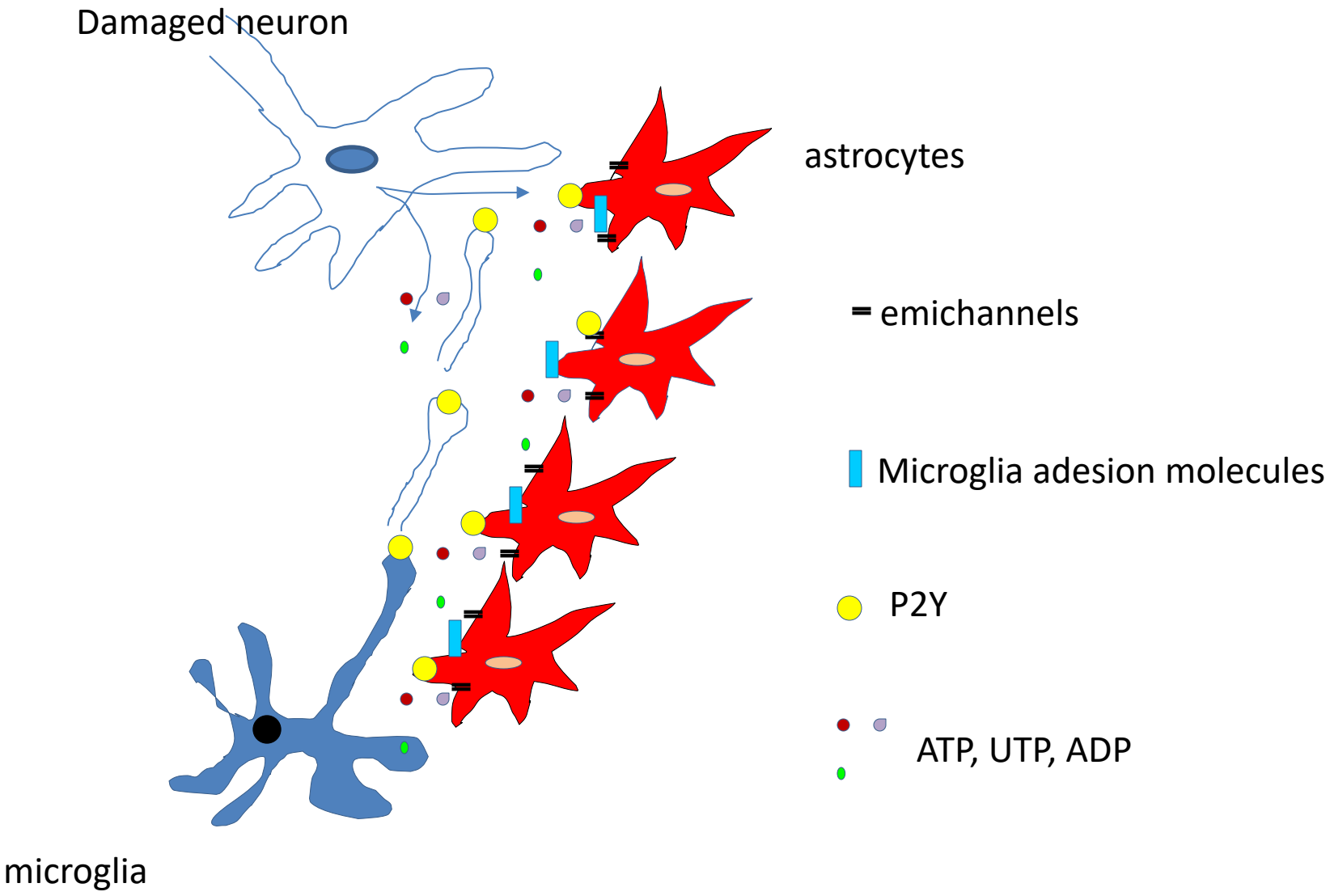


MICROGLIA

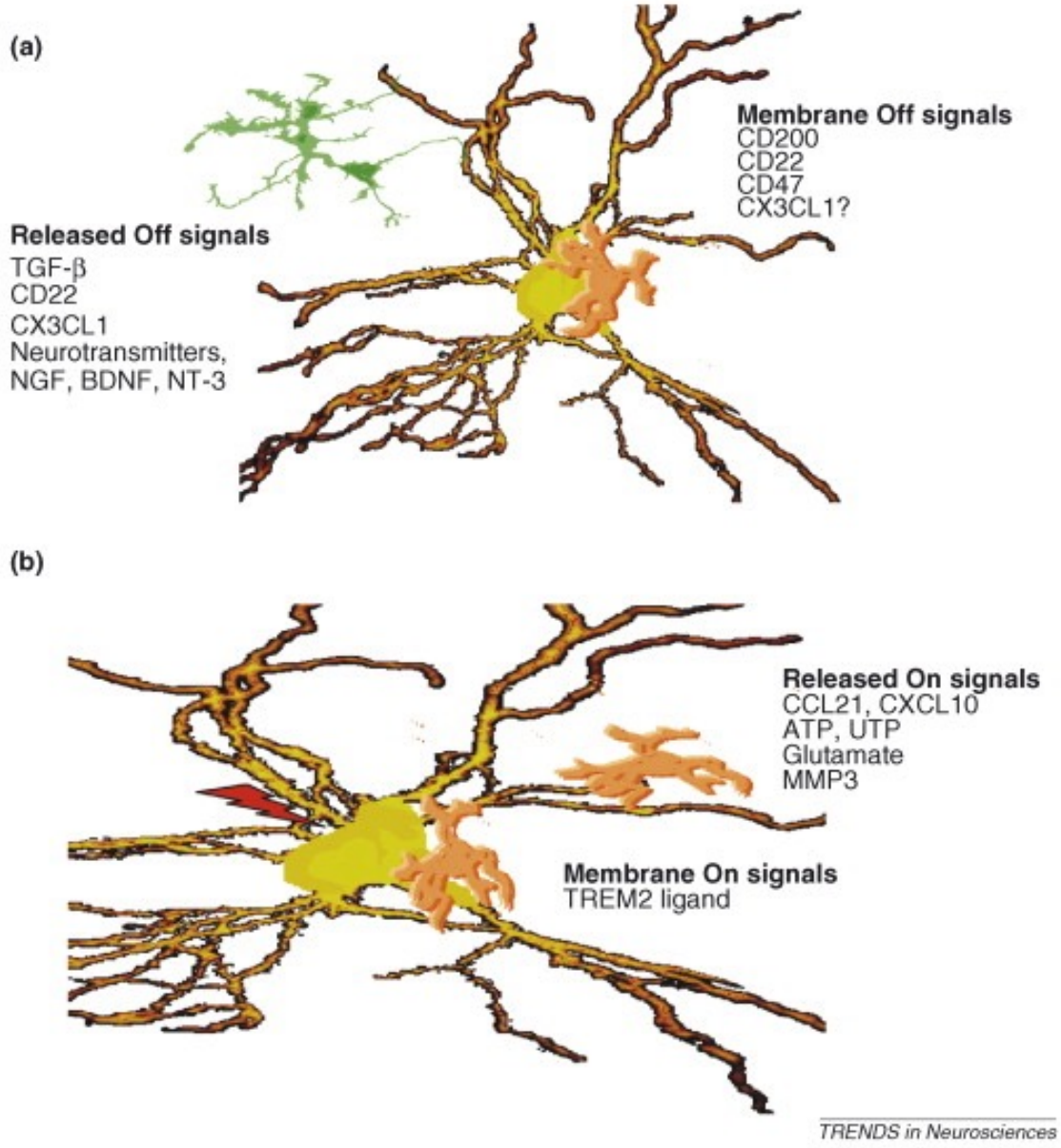


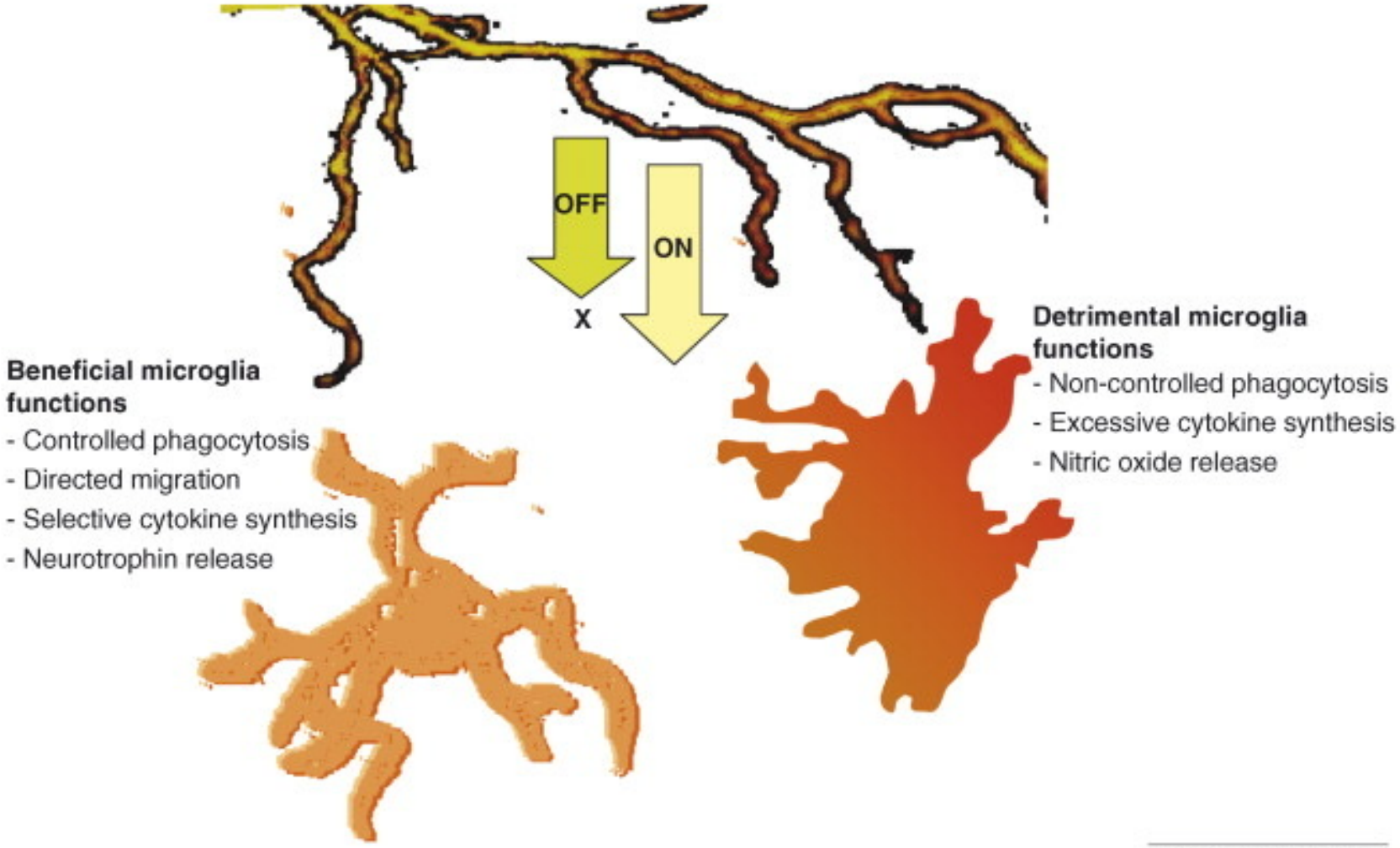

Invaders
Immune Cells
Large Molecules
Blood Cells
Surveillance Microglia
Activation
Activated Microglia
Transformation

Microglial branch movement in normal and injured brain.

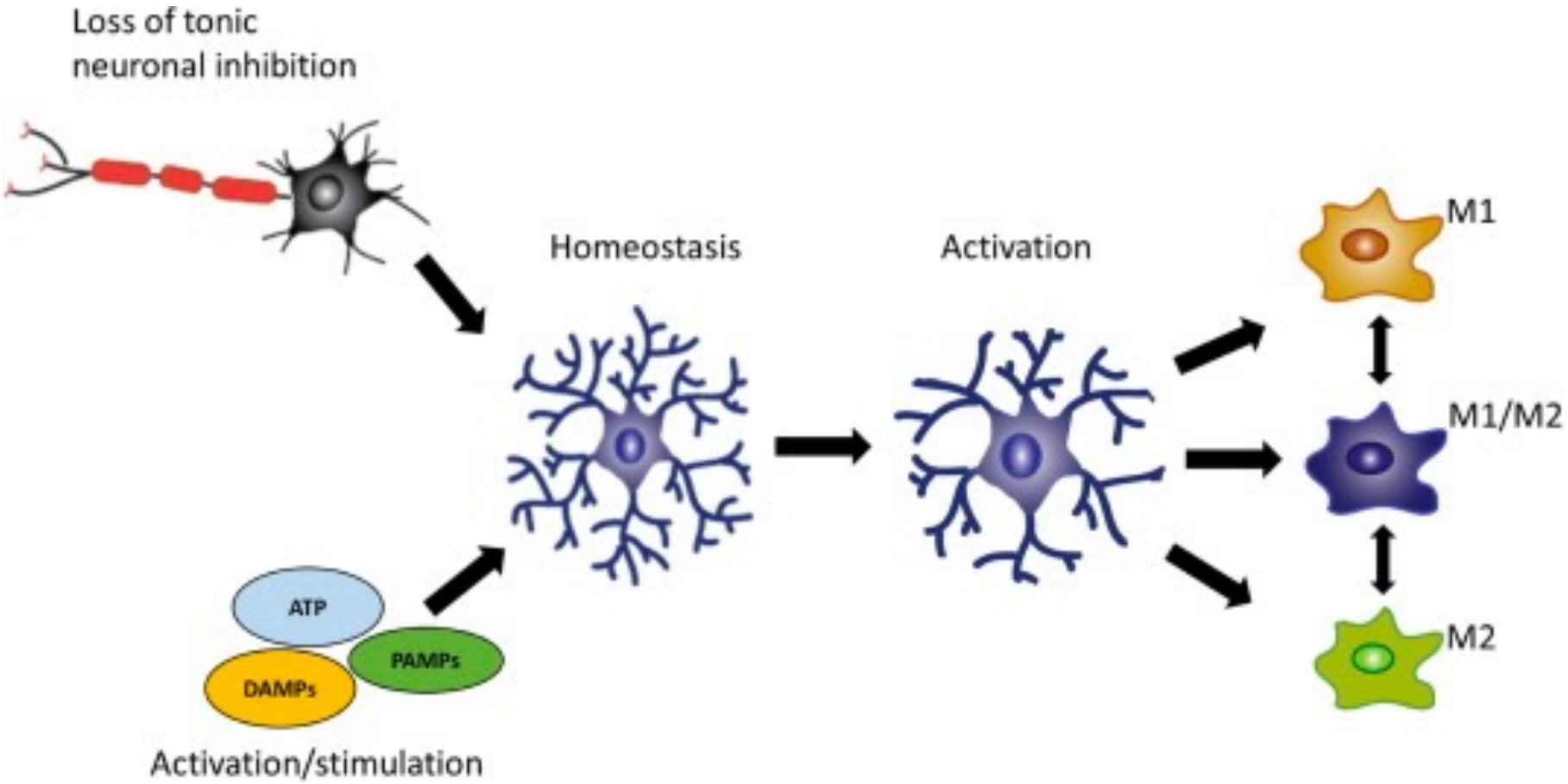


ON and OFF signals control microglia

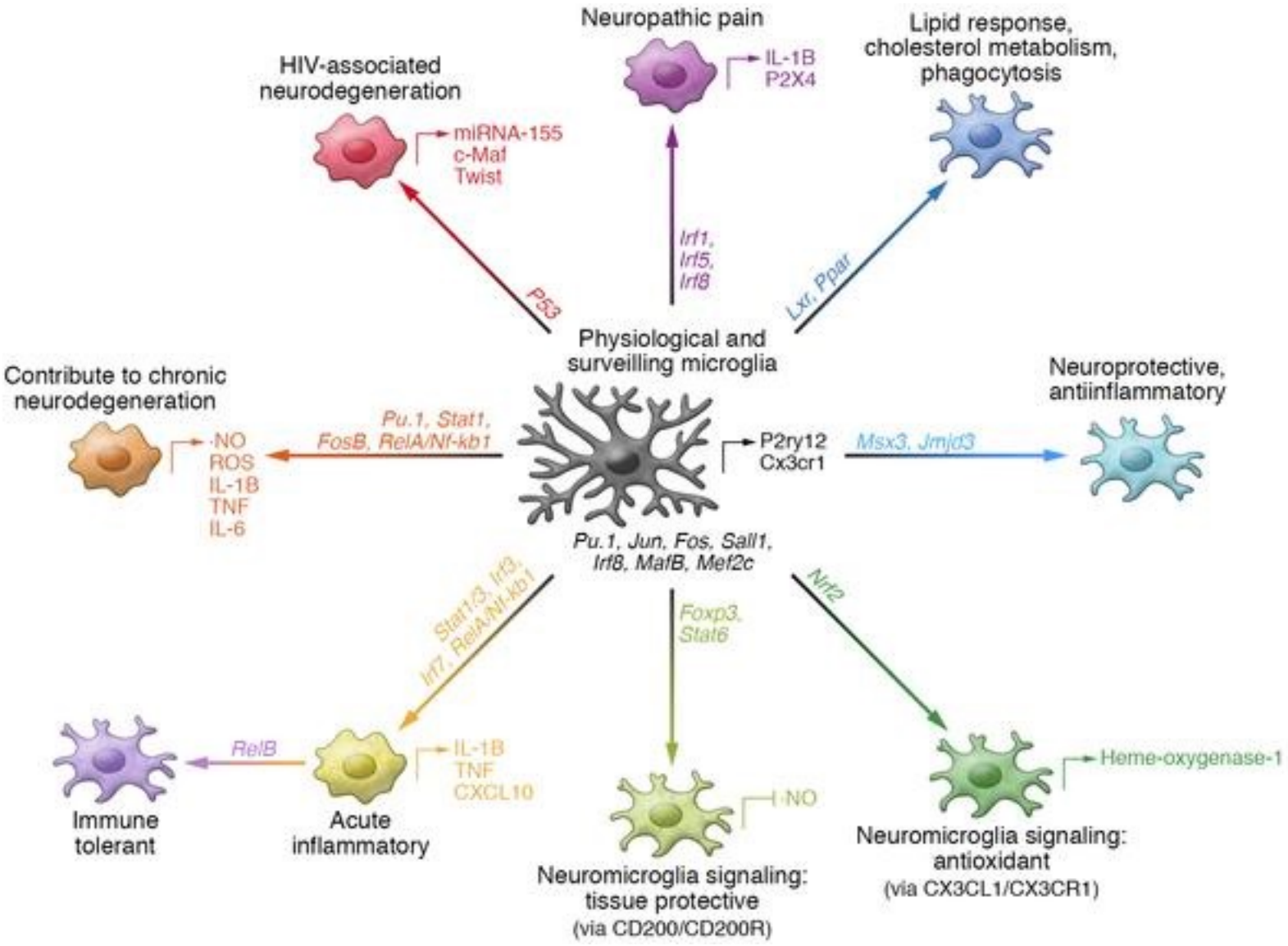



OFF
ON
X
Beneficial microglia functions
- Controlled phagocytosis
- Directed migration
- Selective cytokine synthesis
- Neurotrophin release
Detrimental microglia functions
- Non-controlled phagocytosis
- Excessive cytokine synthesis
- Nitric oxide release
TRENDS in Neurosciences

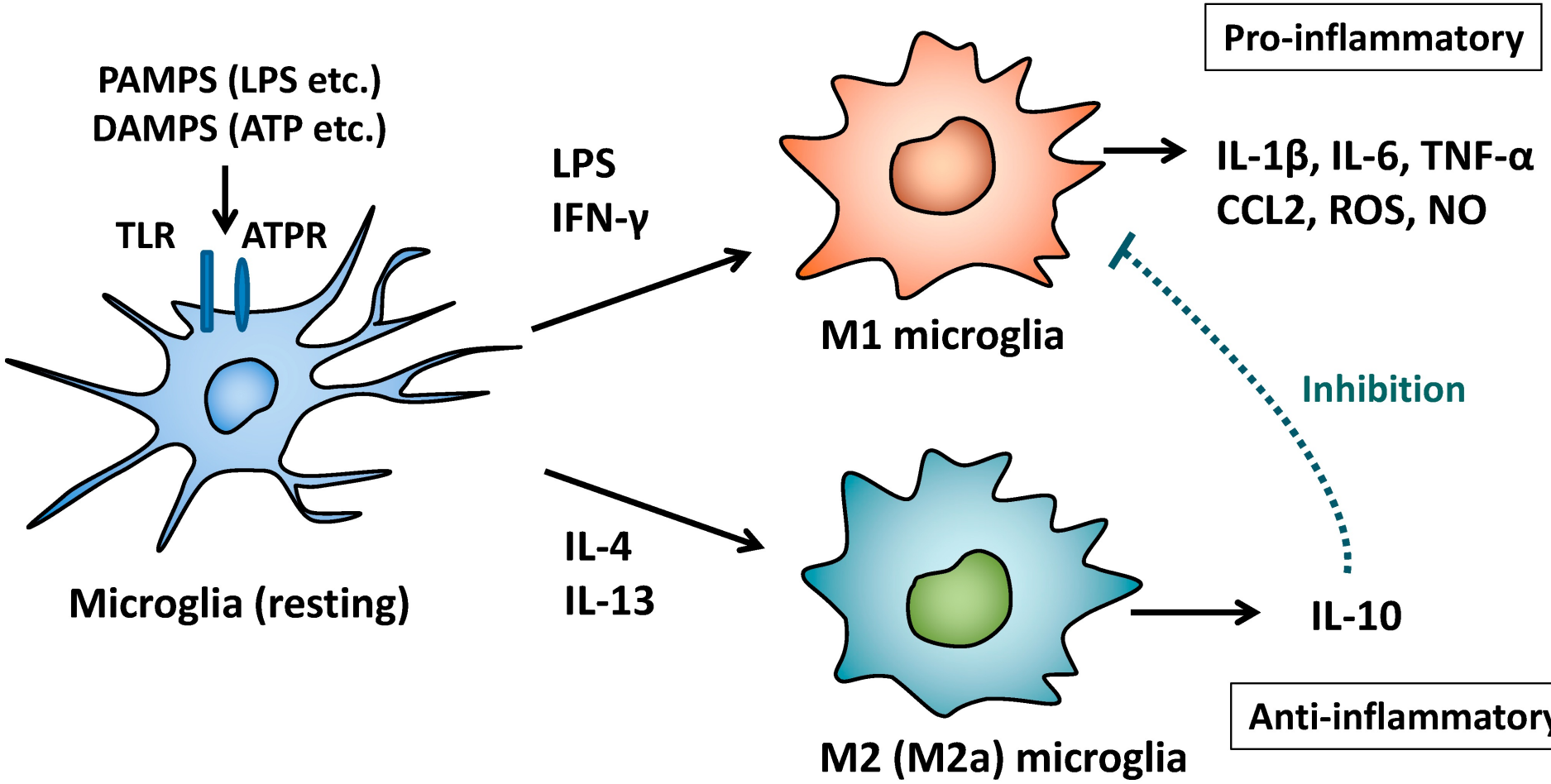
Microglia “activation”



Microglia phenotypes



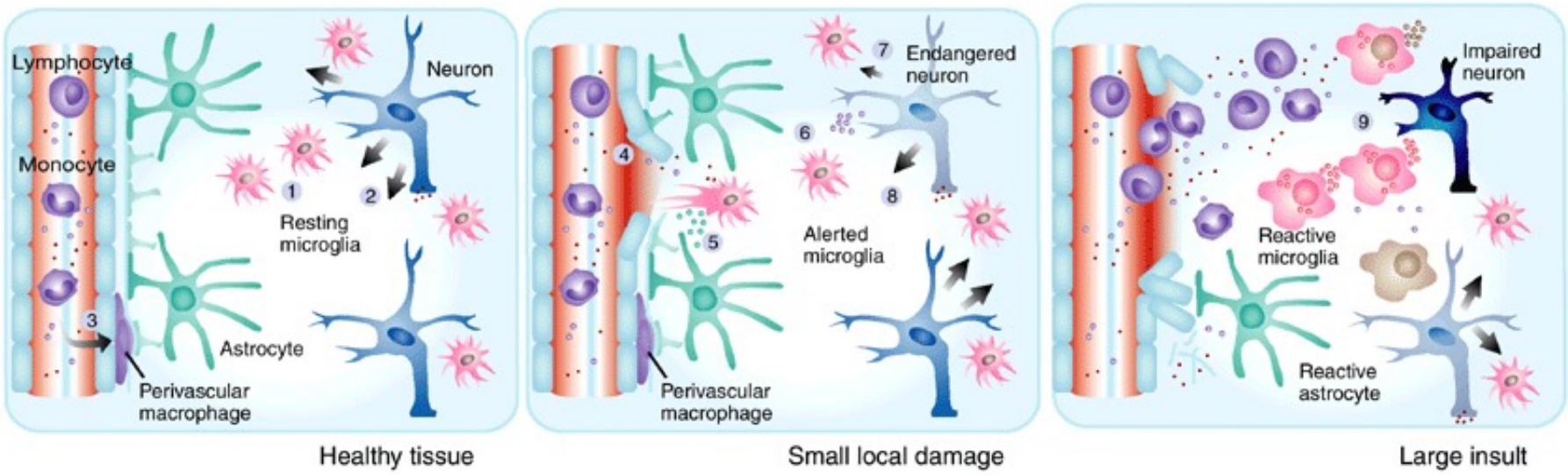
Microglia phenotypes



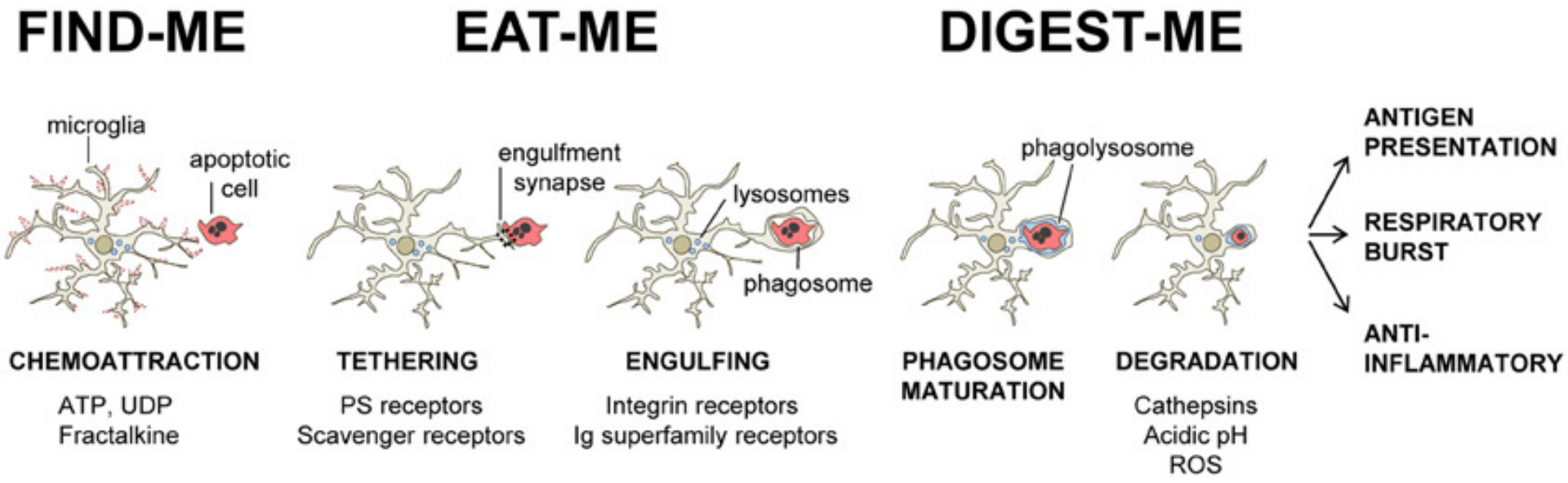
ischemia

- Microgliosis reactive :
  - Local microglia activation
  - Expansion and migration of local microglia
  - Infiltration from the bone marrow of precursors that differentiate into microglia

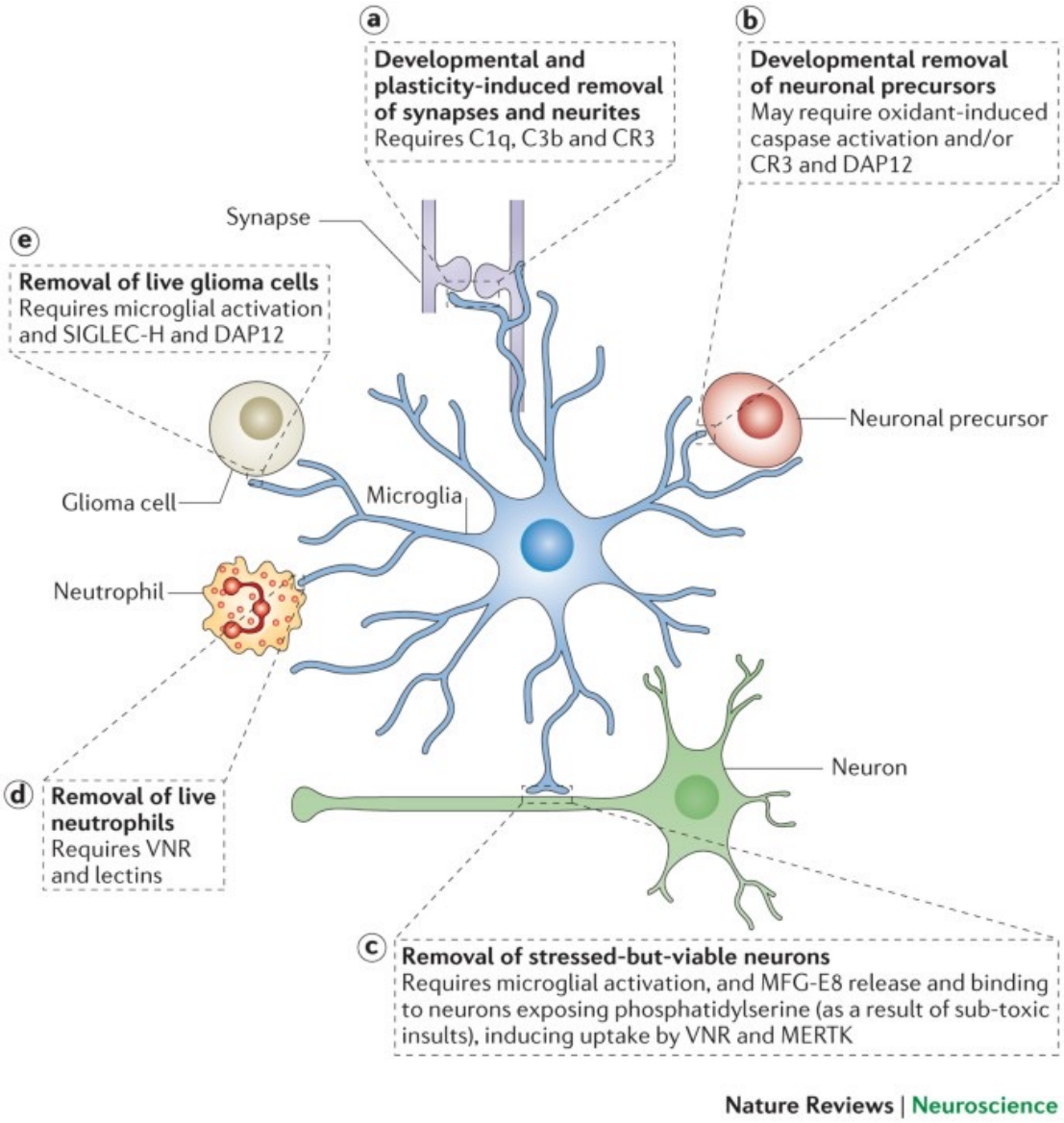
The Journal of Neuroscience, March 7, 2007 • 27(10):2596 –2605
Selective Ablation of Proliferating Microglial Cells Exacerbates Ischemic Injury in the Brain
Melanie Lalancette-Hebert, Genevieve Gowing, Alain Simard, Yuan Cheng Weng, and Jasna Kriz


Lymphocyte
Monocyte
Neuron
1
2
Resting
microglia
3
Astrocyte
Perivascular
macrophage
Healthy tissue
4
5
7
Endangered
neuron
6
8
Alerted
microglia
Perivascular
macrophage
Small local damage
Impaired
neuron
9
Reactive
microglia
Reactive
astrocyte
Large insult
Jessica Iannuzzi

Microglia phagocitosys



Microglia phagocitosys



Damage pattern of the entorhinal cortex

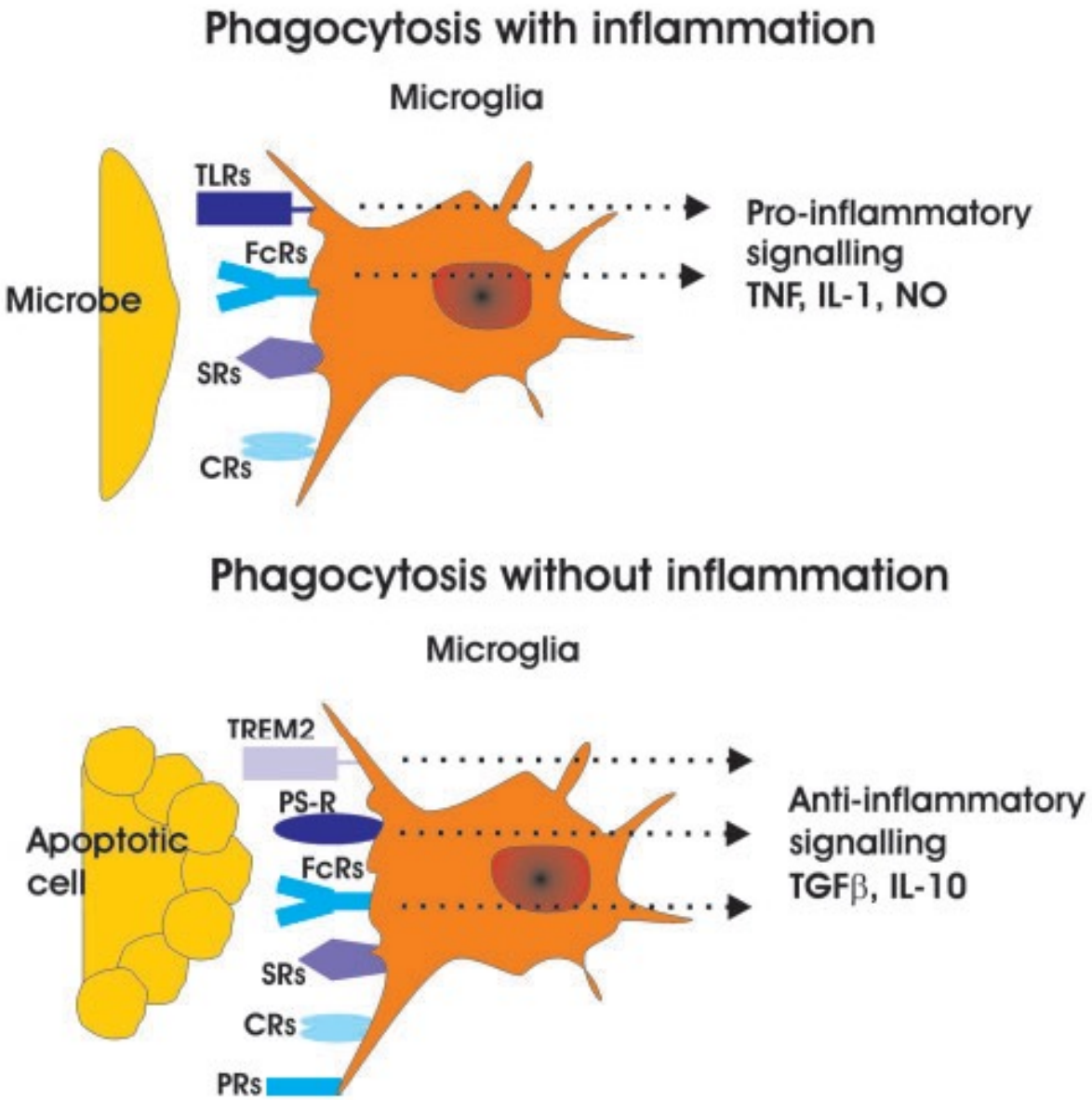
- Axonal damageMicroglial migration (3 d)
- Dendritic degeneration (8 d)
- MHC I-dependent process

J Neuroscience (2004) 24:8500–8509

CXCR3-Dependent Microglial Recruitment Is Essential for Dendrite Loss after Brain Lesion

A Rappert, I Bechmann, T Pivneva, J Mahlo, K Biber, C Nolte, A D. Kovac, C Gerard, HWGM Boddeke, R Nitsch, and H Kettenmann

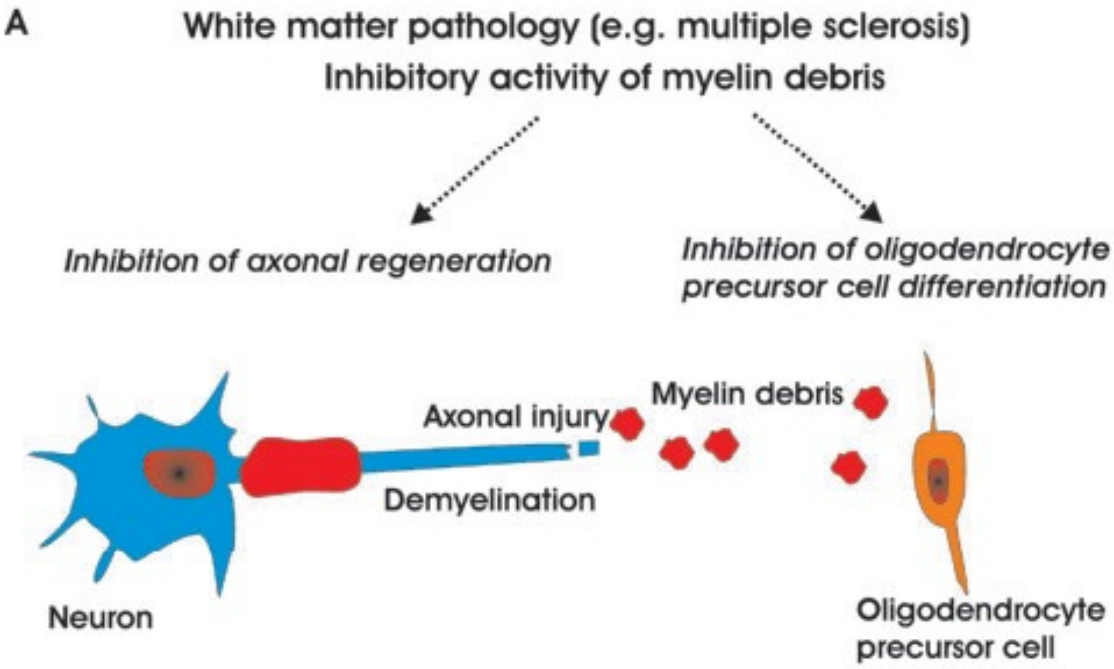
Receptors involved in µglia phagocytosis

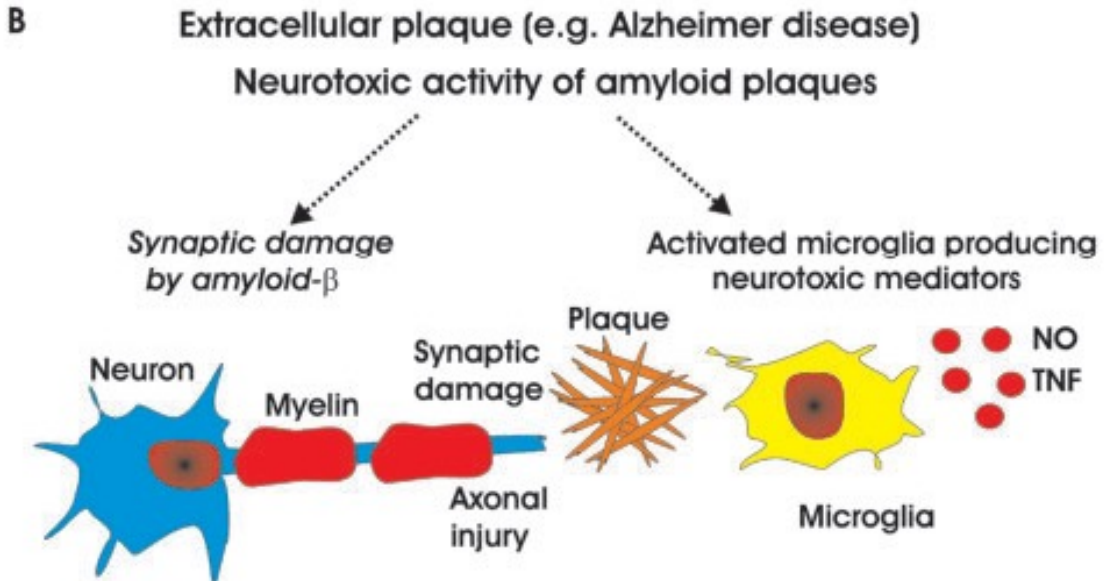


Multiple sclerosis

- Phagocytic cells in the perivascular zones of active inflammatory lesion
- Microglia phagocyte actively detritus of myelin
- EAE improved by the addition of TREM2 + cells (triggering receptor expressed on myeloid cells)

Multiple sclerosis





Microglia in Alzheimer's disease

- Proliferation and activation of microglia in the brain, concentrated around amyloid plaques, is a prominent feature of Alzheimer's disease (AD).

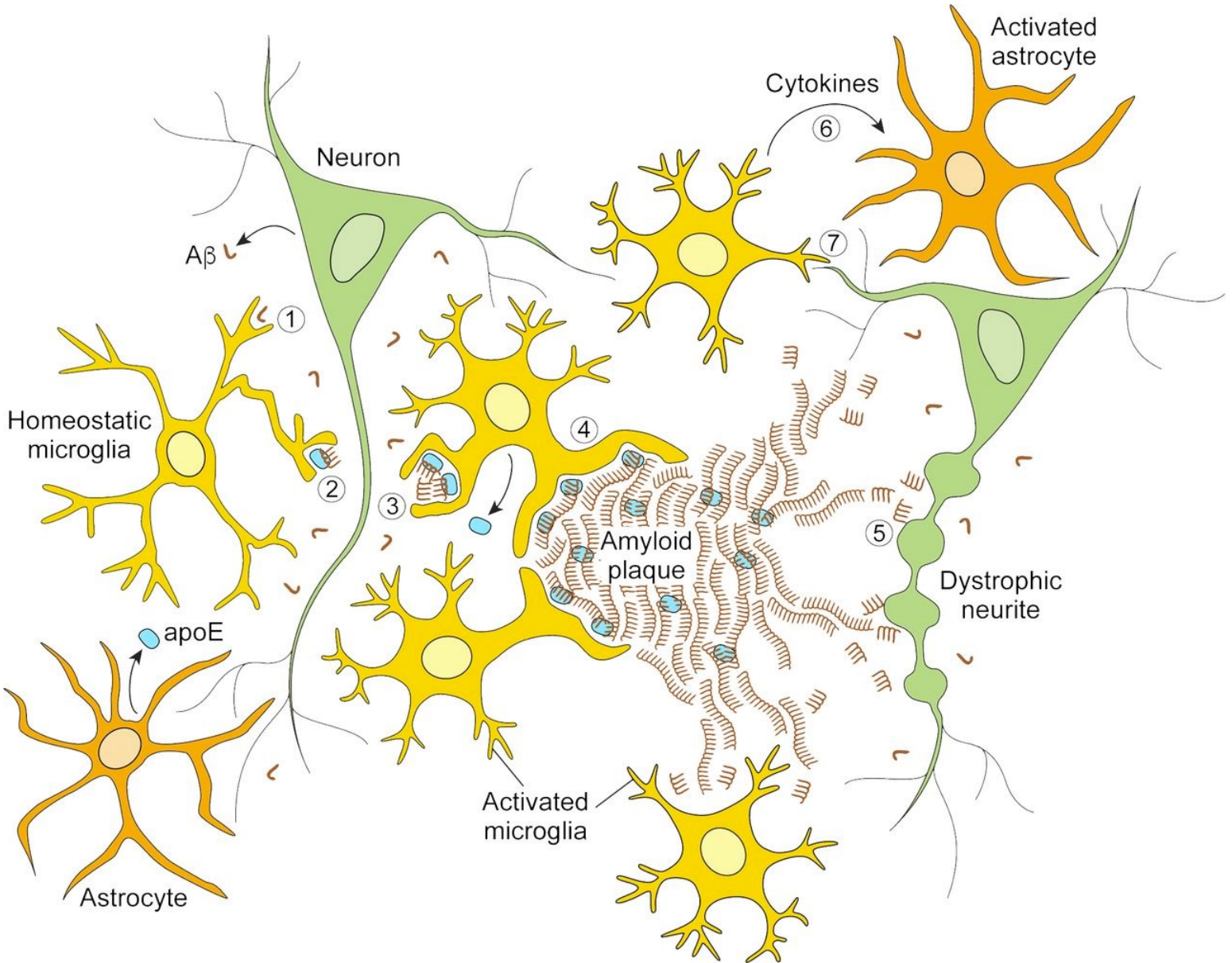
- Human genetics data point to a key role for microglia in the pathogenesis of AD. The majority of risk genes for AD are highly expressed (and many are selectively expressed) by microglia in the brain.

- There is mounting evidence that microglia protect against the incidence of AD, as impaired microglial activities and altered microglial responses to β-amyloid are associated with increased AD risk.

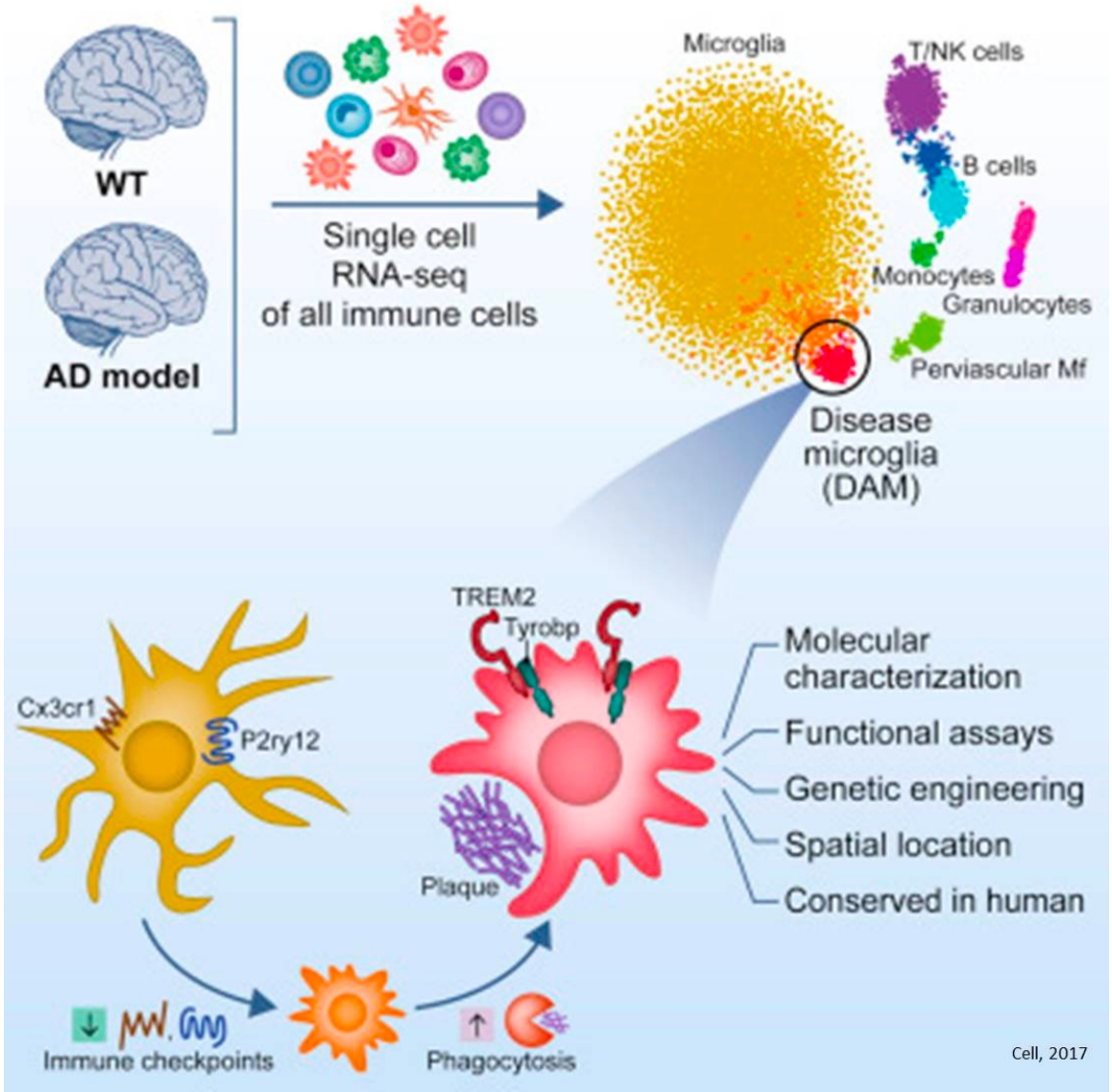
- On the other hand, there is also abundant evidence that activated microglia can be harmful to neurons. Microglia can mediate synapse loss by engulfment of synapses, likely via a complement-dependent mechanism; they can also exacerbate tau pathology and secrete inflammatory factors that can injure neurons directly or via activation of neurotoxic astrocytes.

- Gene expression profiles indicate multiple states of microglial activation in neurodegenerative disease settings, which might explain the disparate roles of microglia in the development and progression of AD pathology.

Microglia in Alzheimer's disease



Microglia in Alzheimer's disease



Microglia in Brain Tumors

- Glioblastoma is the most common and most malignant primary adult human brain tumour.
- Treatment resistance and tumour recurrence are the result of both cancer cell proliferation and their interaction with the tumour microenvironment.

- A large proportion of the tumour microenvironment consists of an inflammatory infiltrate predominated by microglia and macrophages, which are thought to be subverted by glioblastoma cells for tumour growth.

- Thus, glioblastoma-associated microglia and macrophages are logical therapeutic targets..

Microglia in Brain Tumors