Neurotroxic vs neuroprotective Glia functions

Neurotoxic Glia

Types of neurotoxicity

- Microglia — neurotoxic cytokine release
  ROS

- Astrocytes — astrogliosys, Glu uptake reduction
  Glu, tumorigenesis

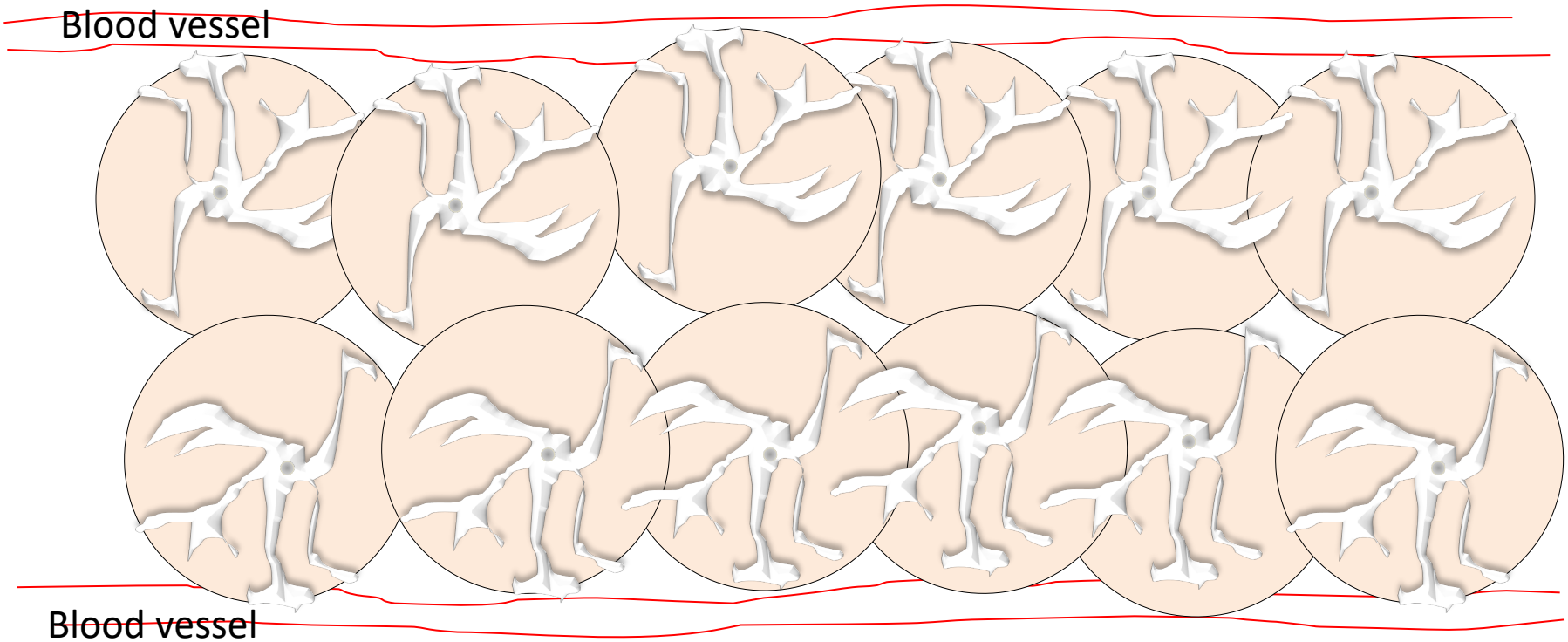
Astrocytes

- Regulate neuronal migration during CNS development (radial glia)
- Regulate synaptogenesis and the maintenance of synapses
- Structural function through the creation of cellular domains
- Together with the endothelial cells they form the BBB
- Regulate cerebral microcirculation (functional hyperemia)

Homeostatic functions of astrocytes

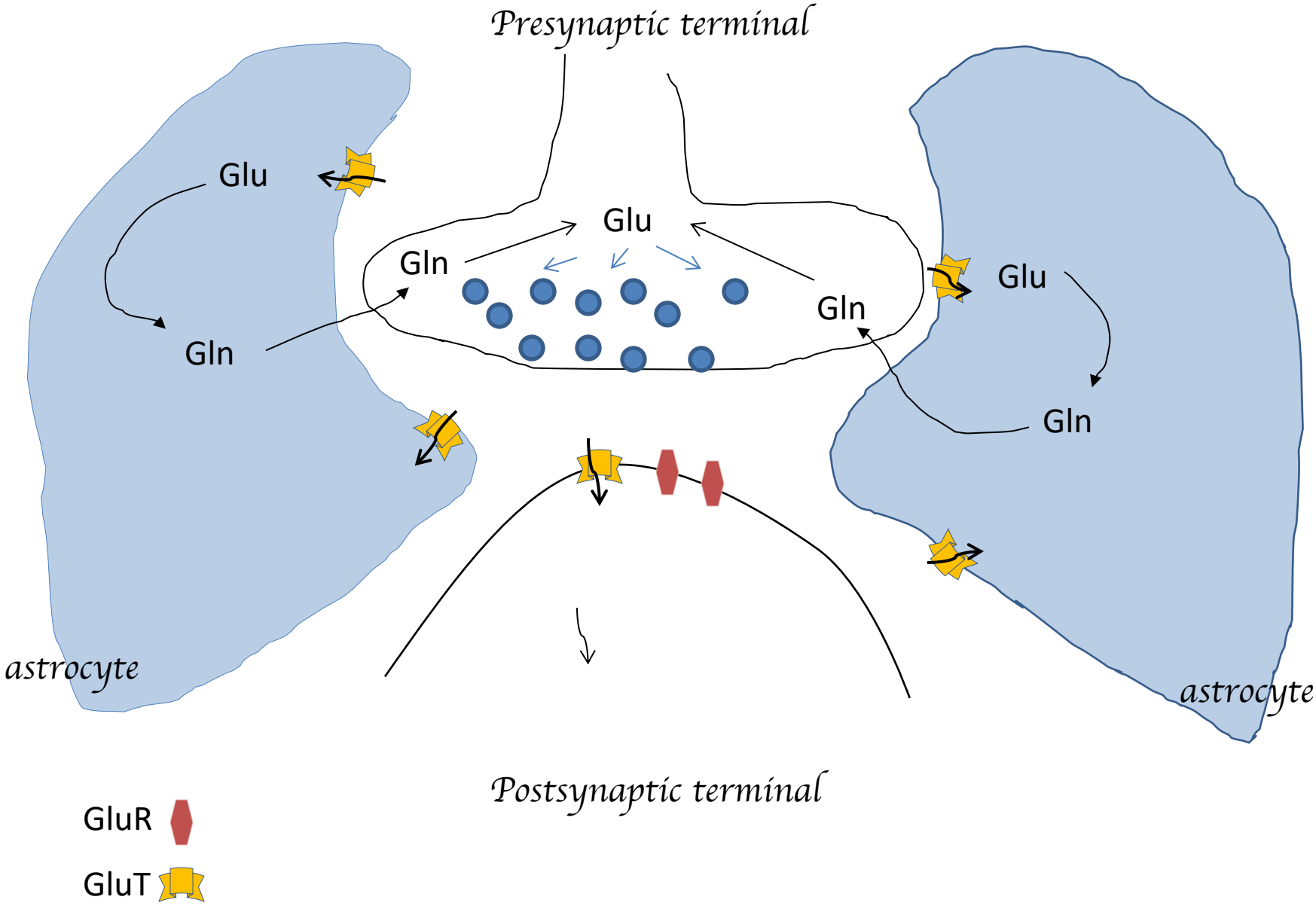
- Homeostasis of electrolytes :
  - K^+
  - Cl^-
  - Ca^{2+}
  - H^+
  - Glutamate homeostasis
  - Homeostasis volume

Astrocytes

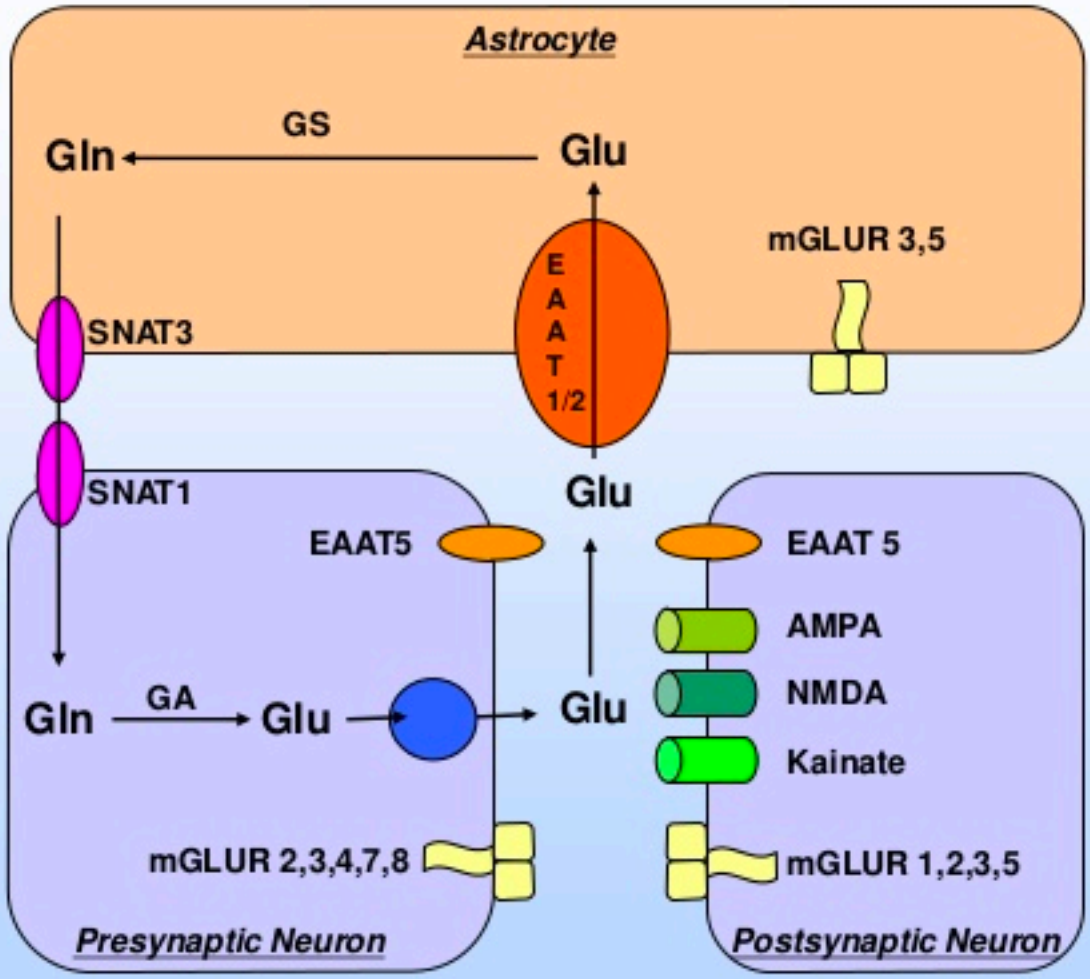


Each astrocyte establishes its territory or domain

Glutamate homeostasis

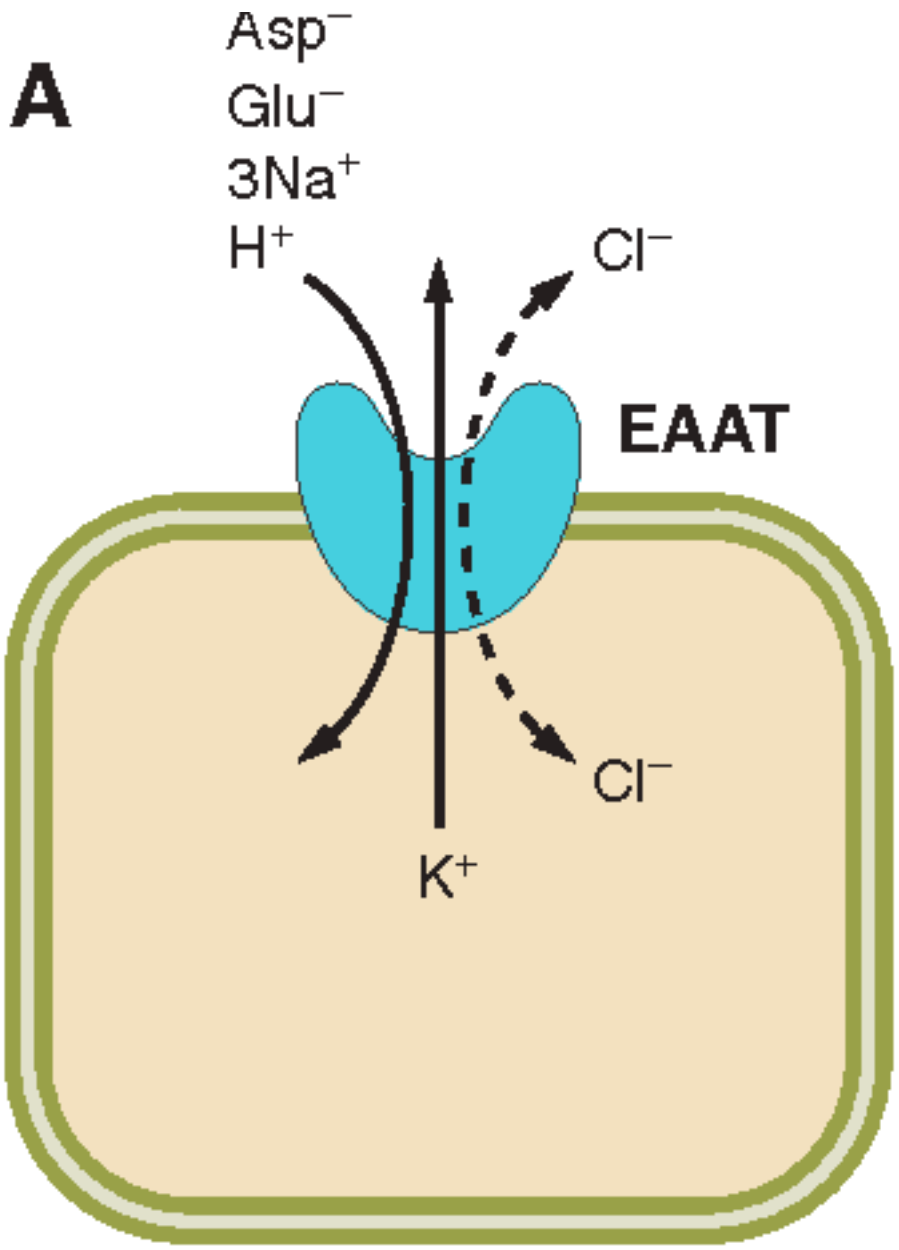


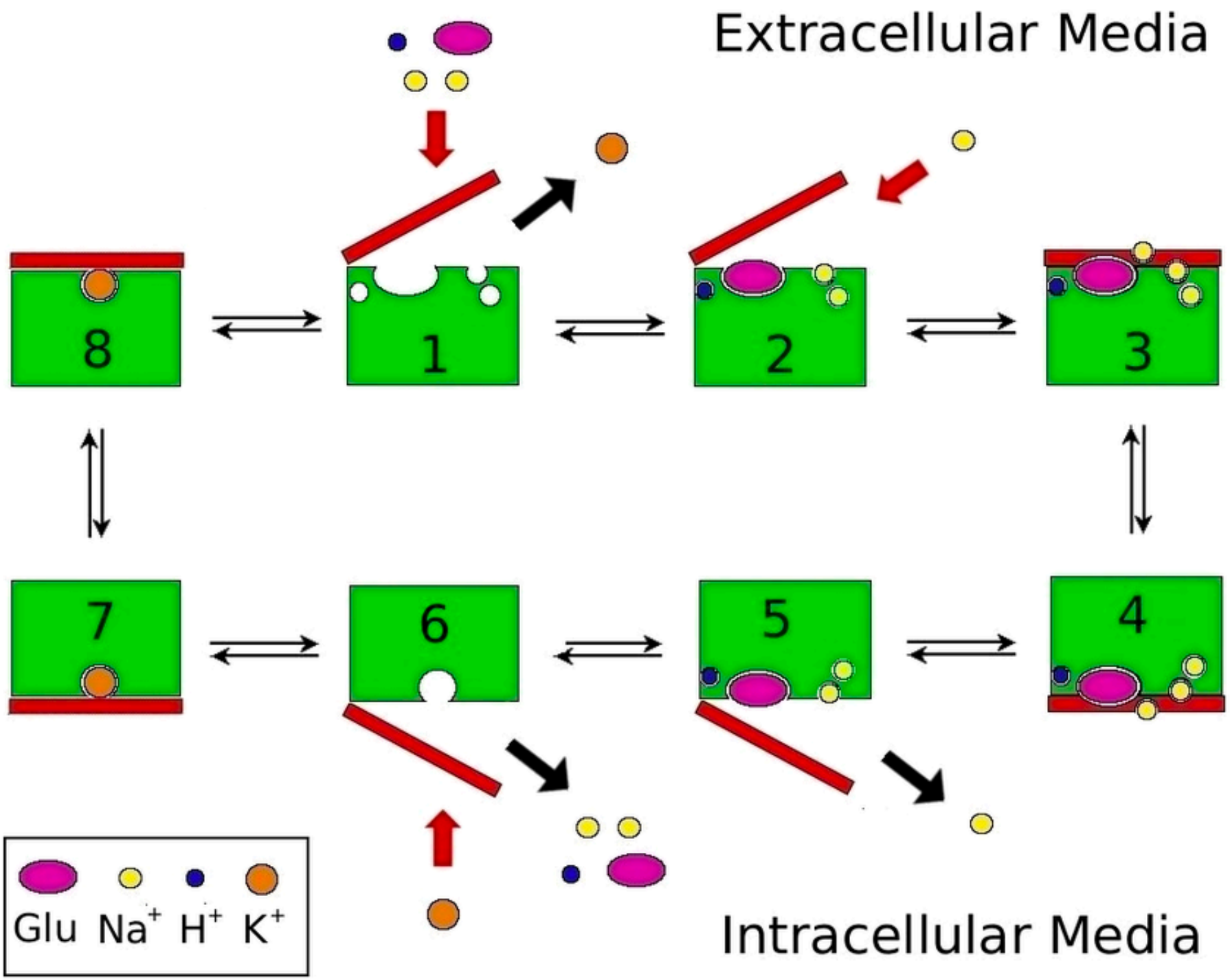
Glutamate-Glutamine Cycle



Glu=glutamate; Gln=glutamine; EAAT= Excitatory Amino Acid Transporter; SNAT= sodium-coupled neutral amino acid transporter; mGLUR= metabotropic glutamate receptors; AMPA= α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; NMDA= N-methyl-D-aspartate receptor; Kainate=kainate receptor; GS=glutamine synthetase; GA=glutaminase;

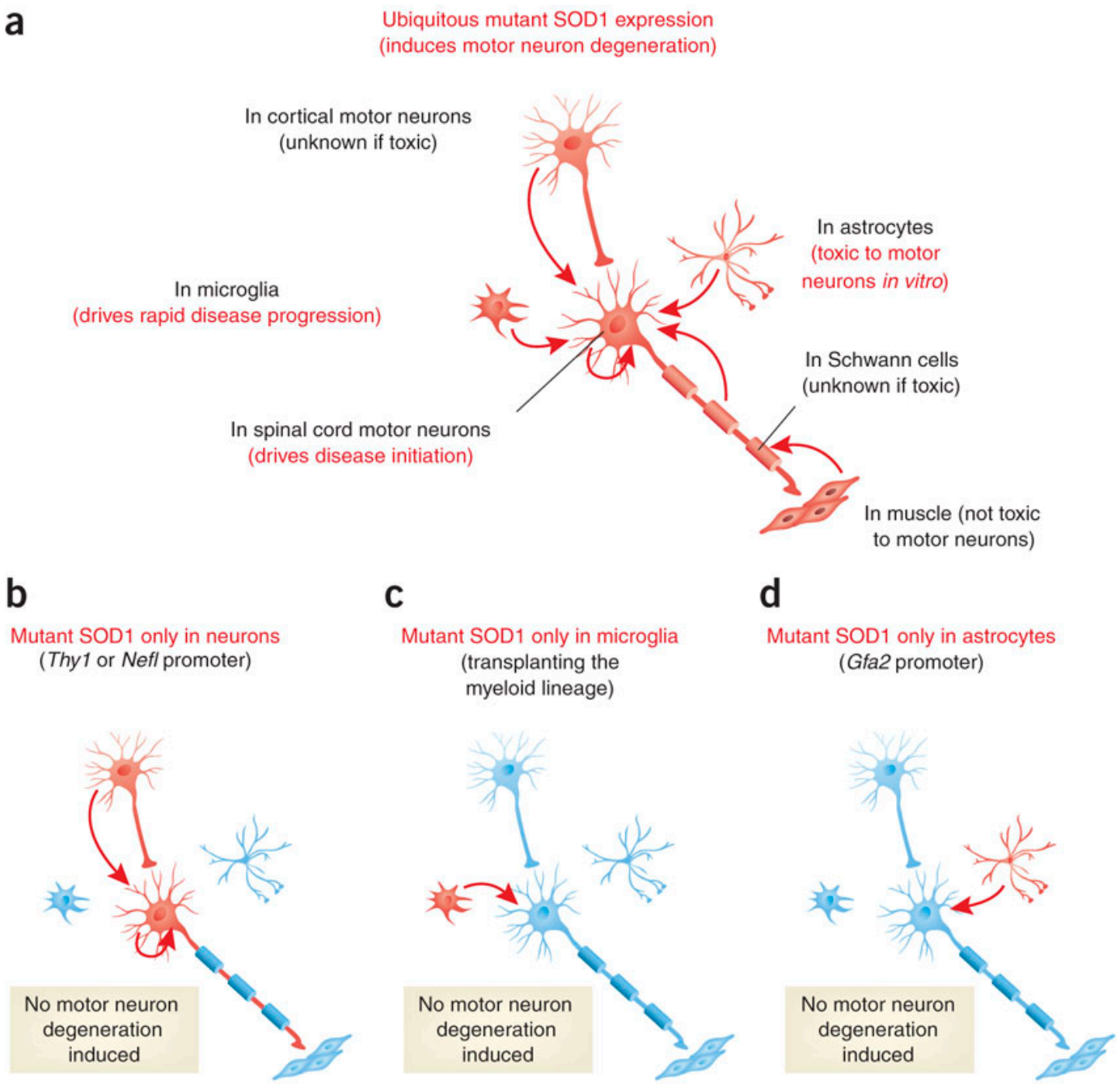
Excitatory Amino Acid Transporters




Extracellular Media
8
1
2
3
7
6
5
4
Glu
Na+
H+
K+
Intracellular Media

Glia-mediated neurotoxicity in SOD-dependent ALS

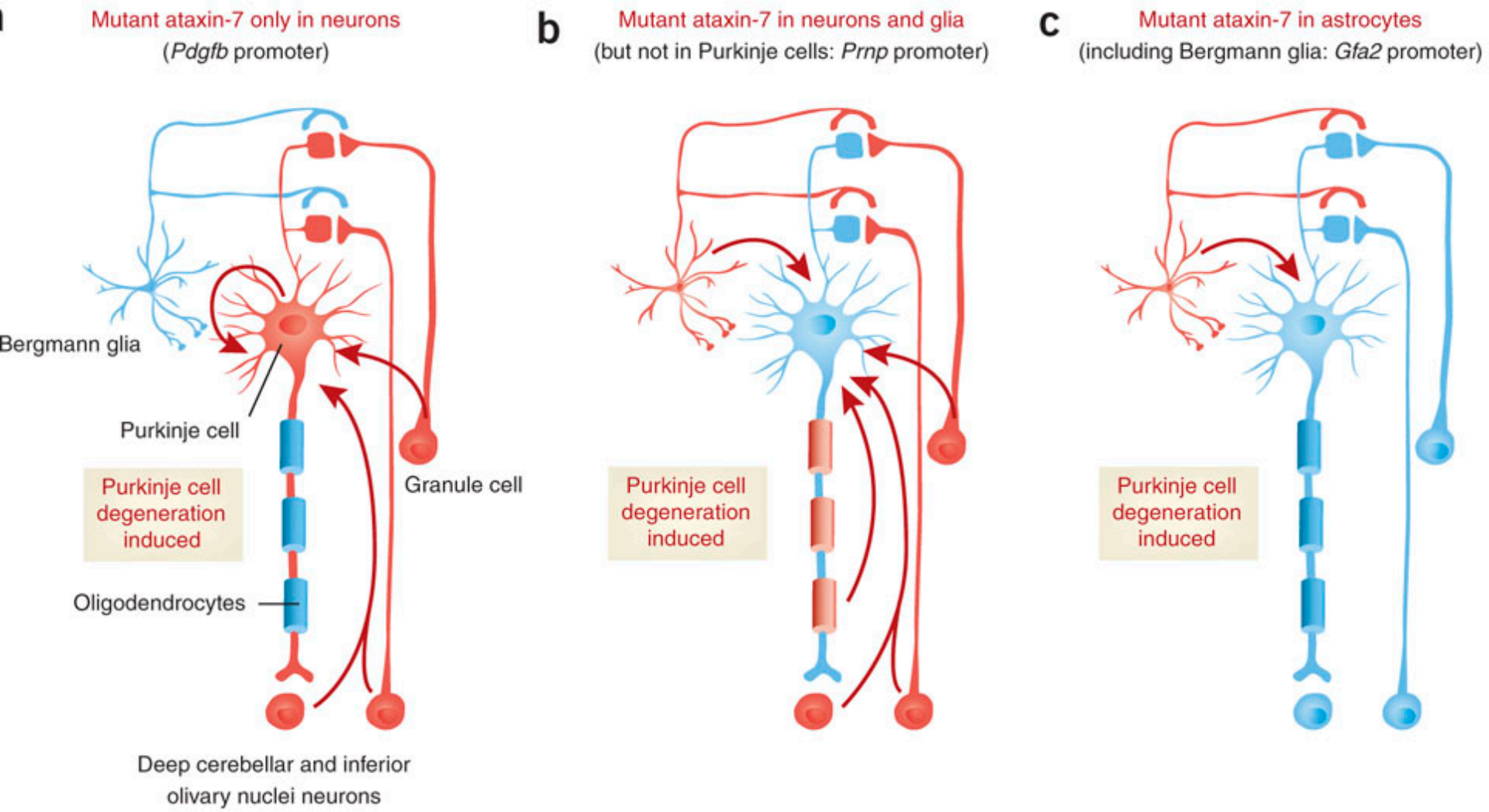
- Patients with ALS develop neuroinflammation (astro- and micro-gliosis)
- microglia^{mut} produces ROS (NADPH oxidase)
- astrocytes^{mut} express lower levels of GLT-1
- astrocytes^{mut} express high levels of chromogranin A, which induces release of SOD^{mut} which activates microglia


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

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

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

Glial
in Hungtinton Disease

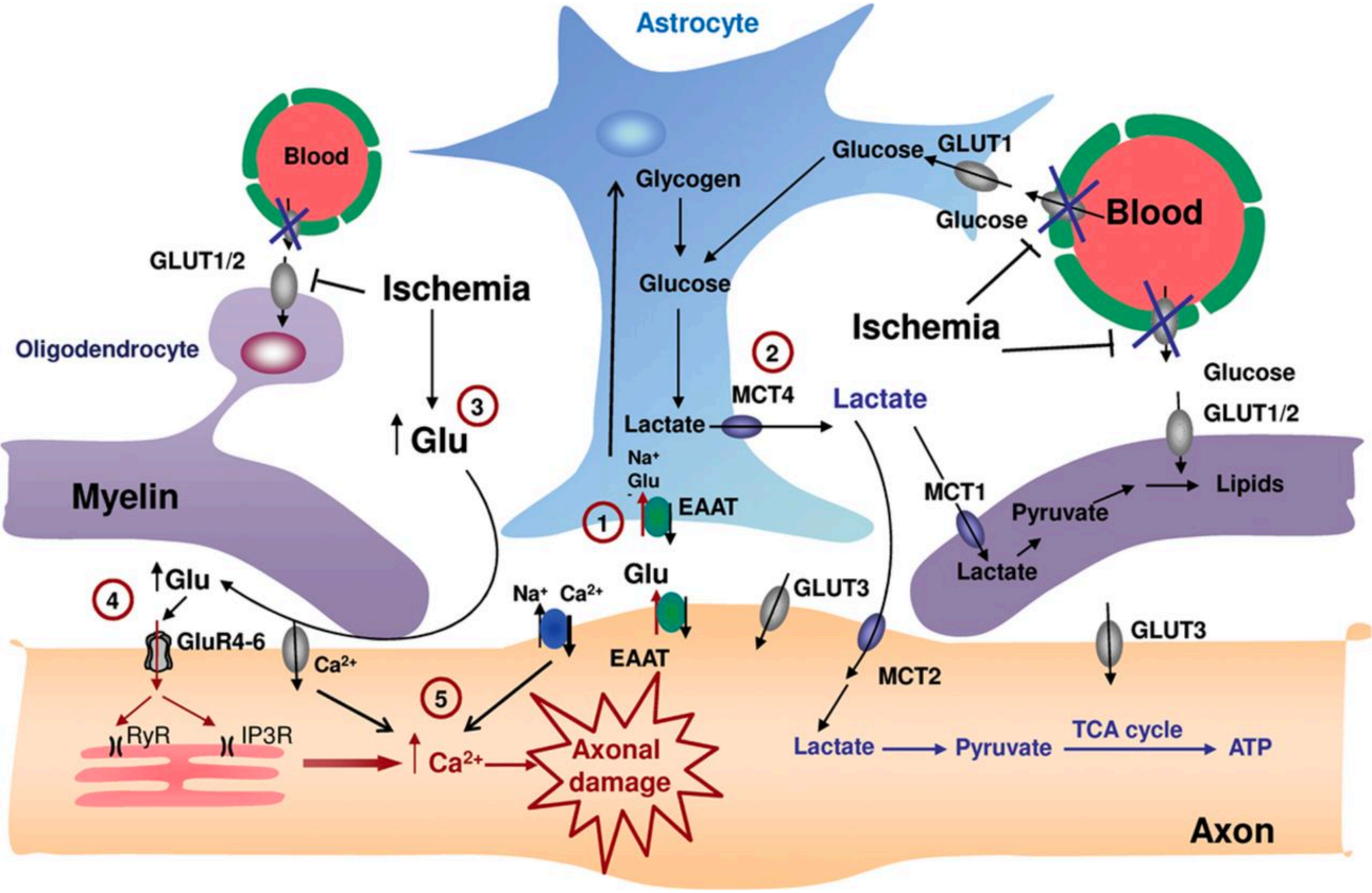
- Indirect evidence of microglial involvement using minocycline

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

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


Astrocyte
Blood
GLUT1/2
Ischemia
Oligodendrocyte
Myelin
Glycogen
Glucose
GLUT1
Glucose
Blood
Ischemia
Glucose
GLUT1/2
Lipids
Pyruvate
Lactate
MCT1
2
MCT4
Lactate
3
Glu
Lactate
Na+
Glu
EAAT
1
4
Glu
GluR4-6
Ca2+
Na+ Ca2+
Glu
EAAT
GLUT3
MCT2
GLUT3
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

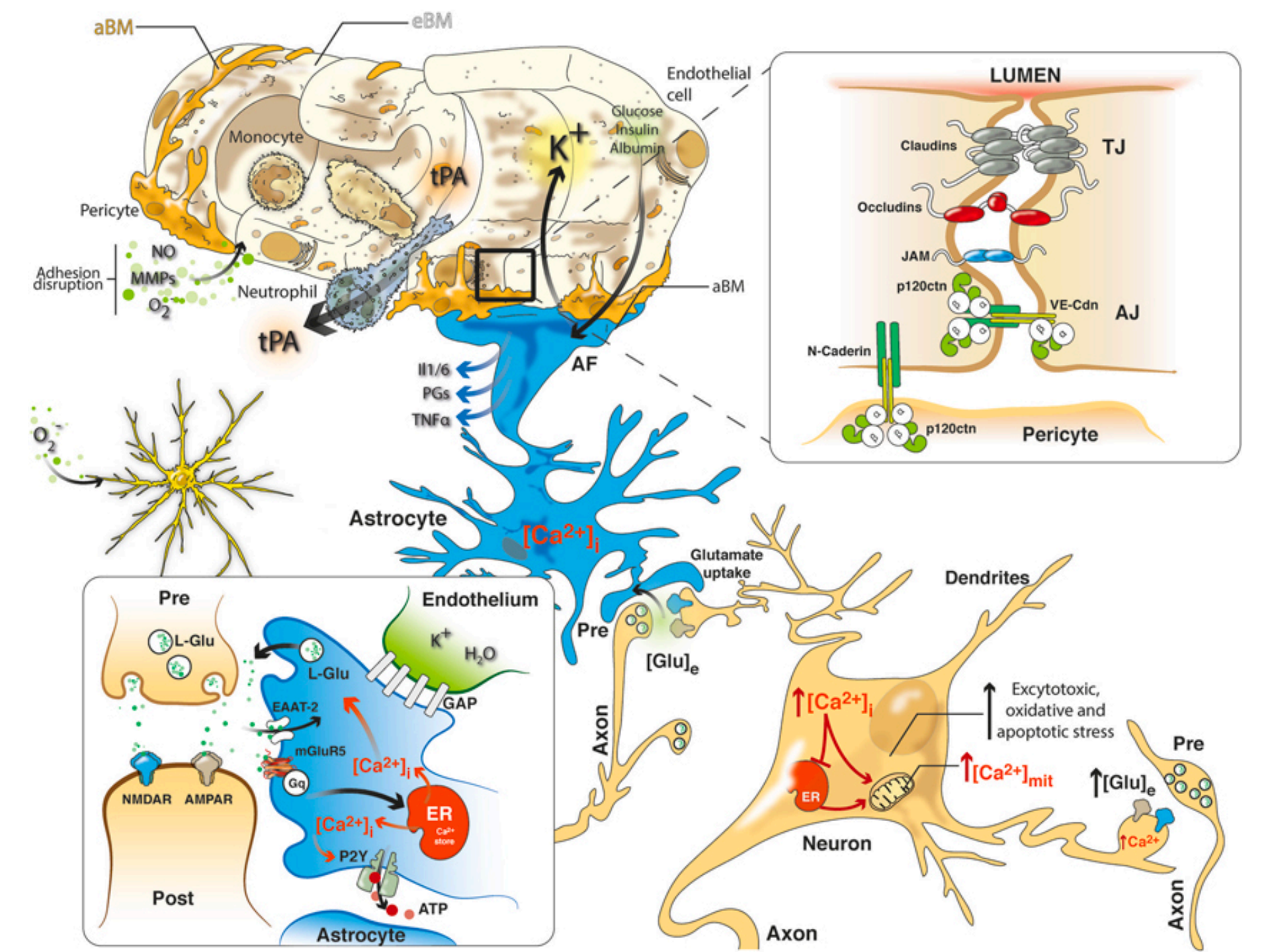
Three mechanisms: 2 Glutamate release

- 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

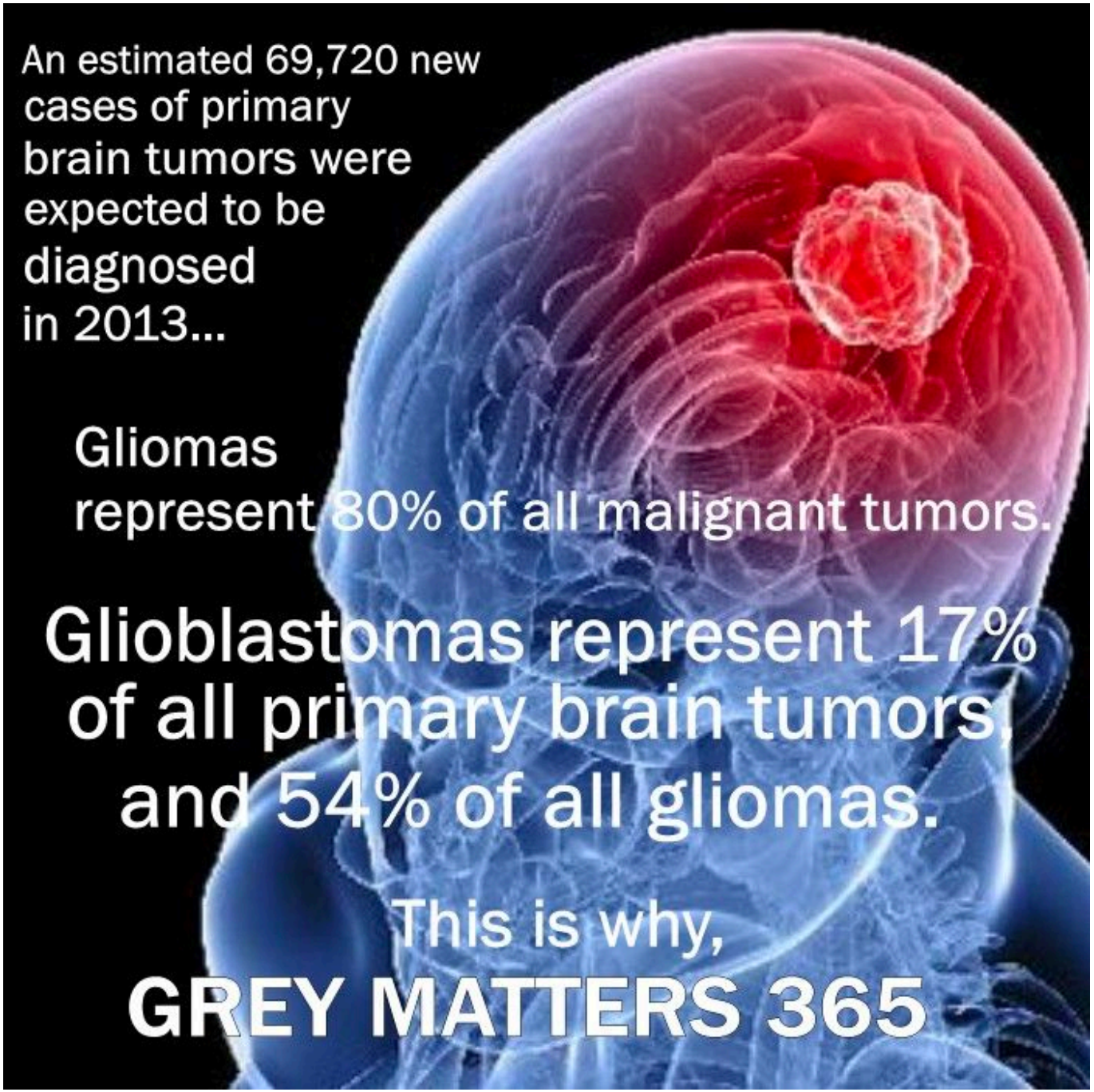
- The gap junctions are closed (partially)

- The emichals open (pass Glu, glutathione)


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

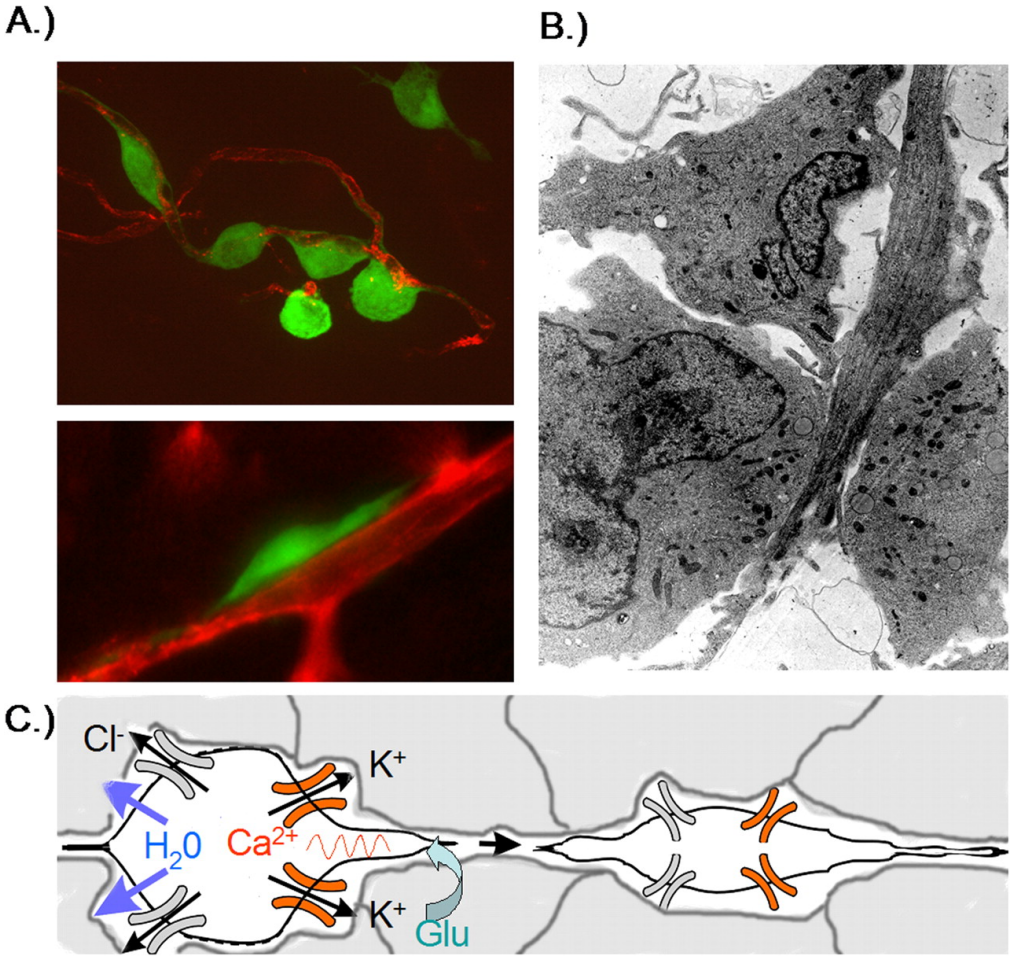

An estimated 69,720 new cases of primary brain tumors were expected to be diagnosed in 2013...
Gliomas represent 80% of all malignant tumors.
Glioblastomas represent 17% of all primary brain tumors, and 54% of all gliomas.
This is why,
GREY MATTERS 365

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

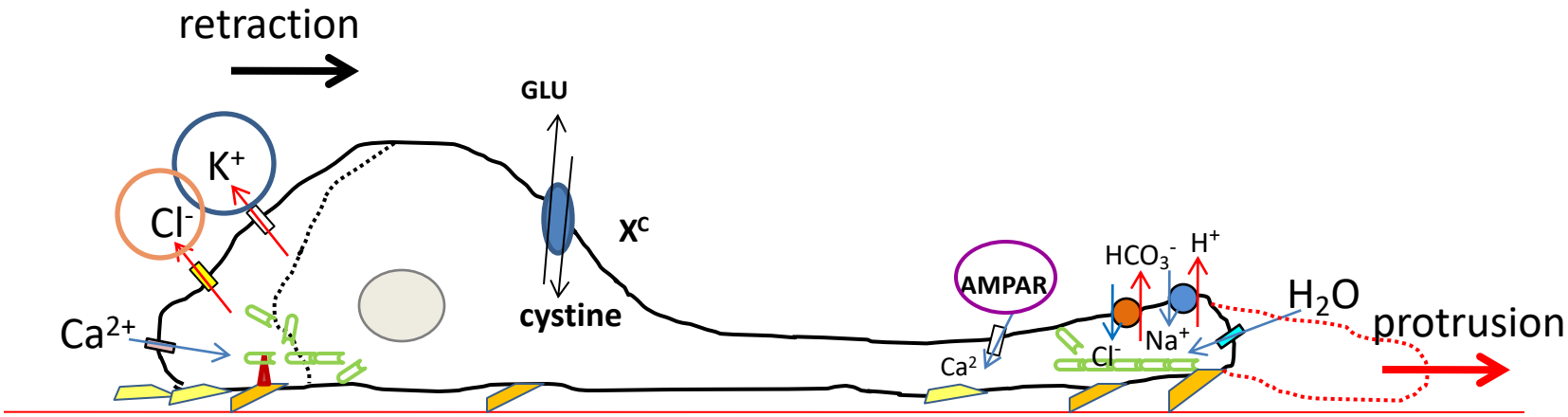


Sontheimer, 2008

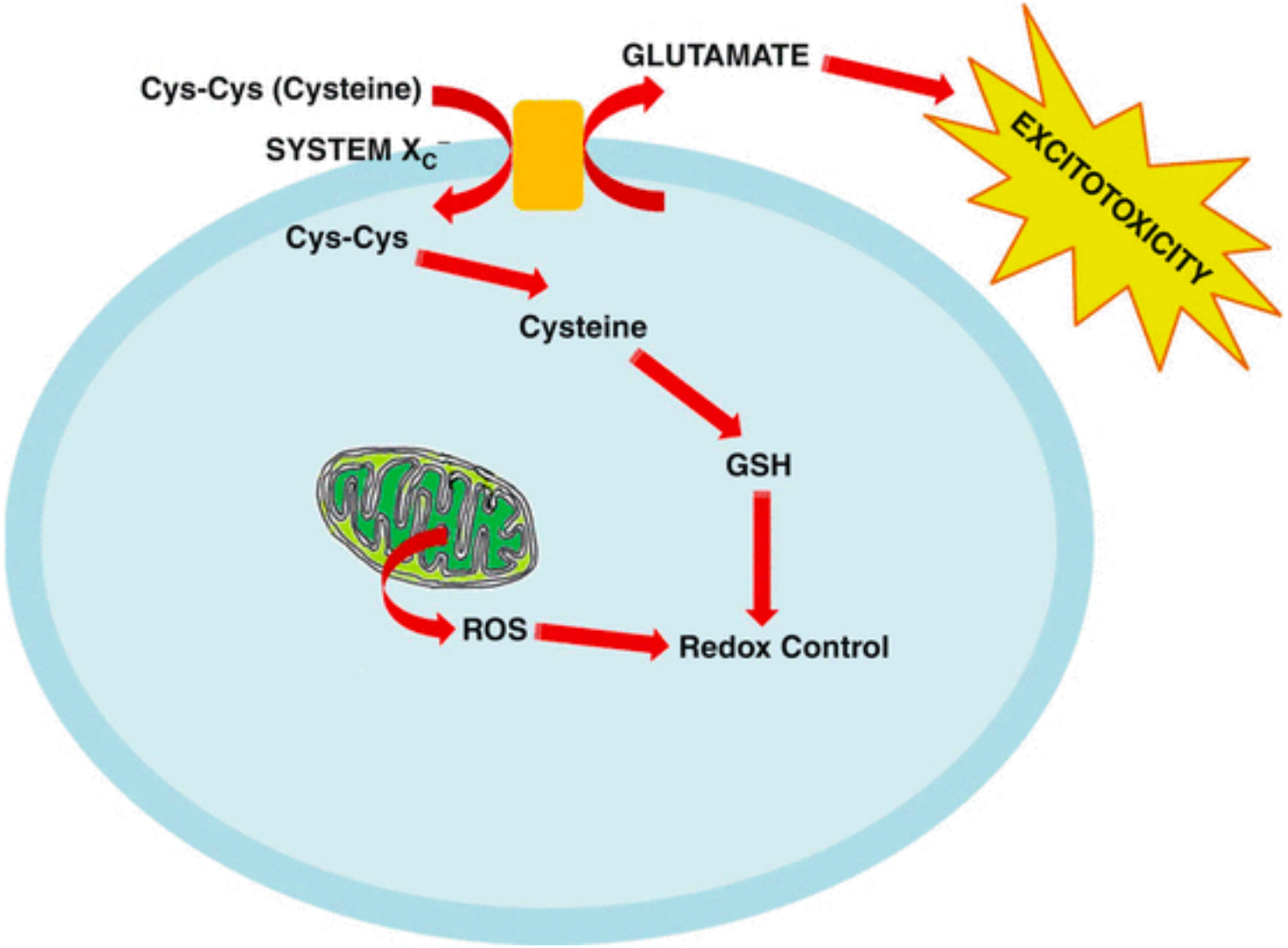
Ion channels involved in glioma migration

- 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



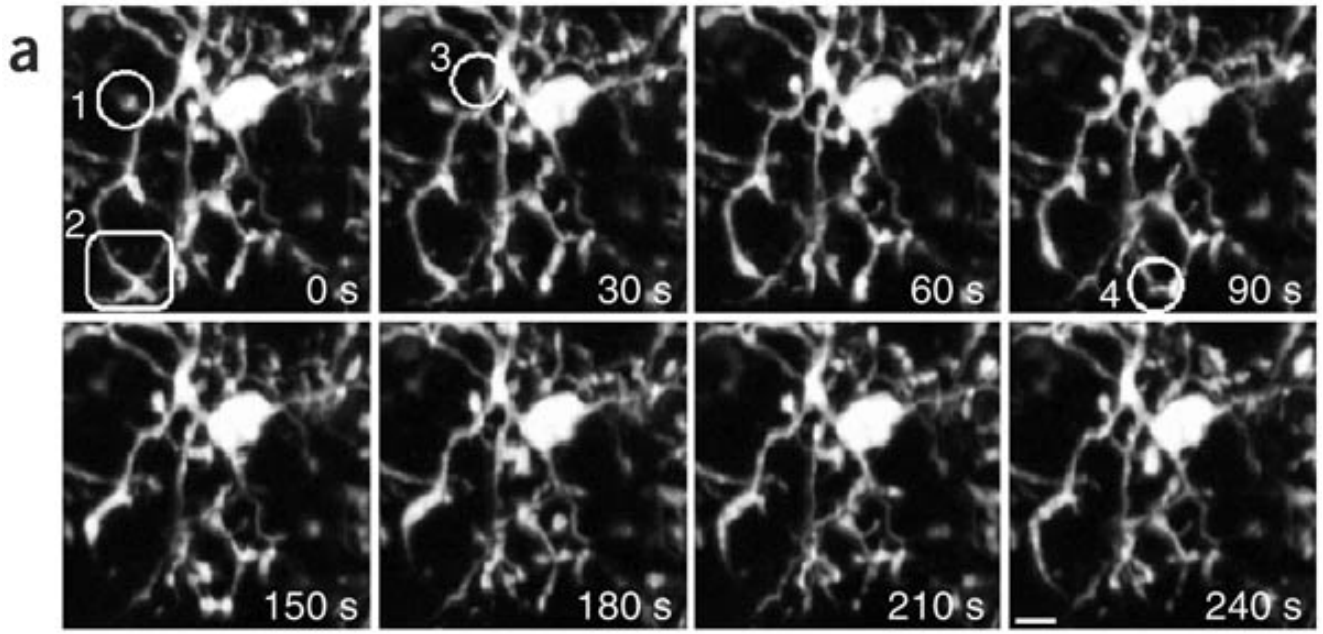
Glioma glutamate release

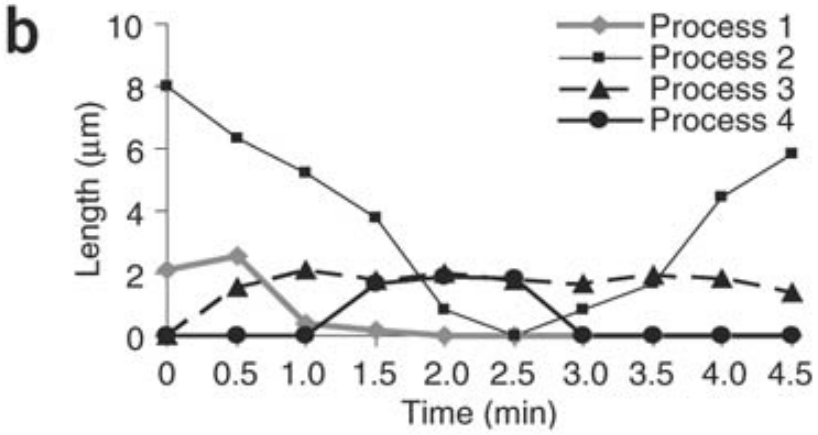


Neuroprotective action of the glia

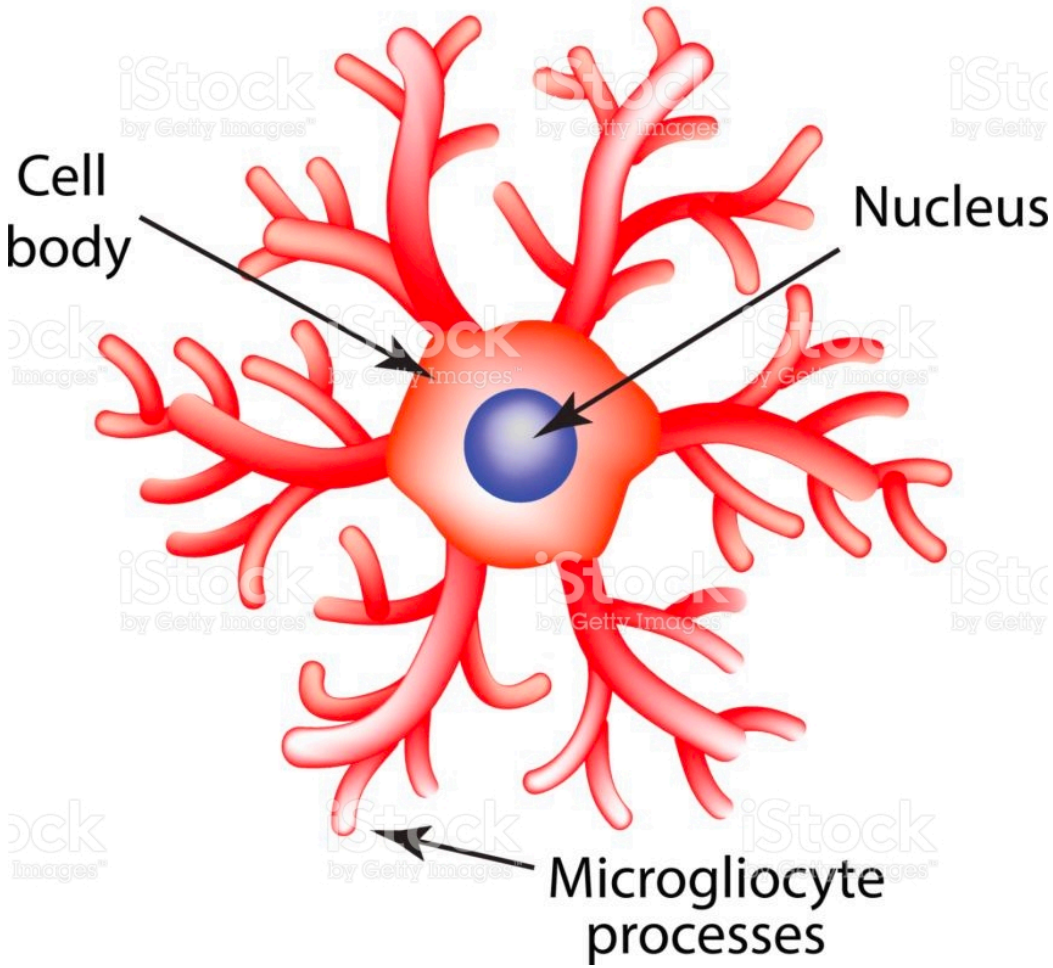
The good and bad of glial activation

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

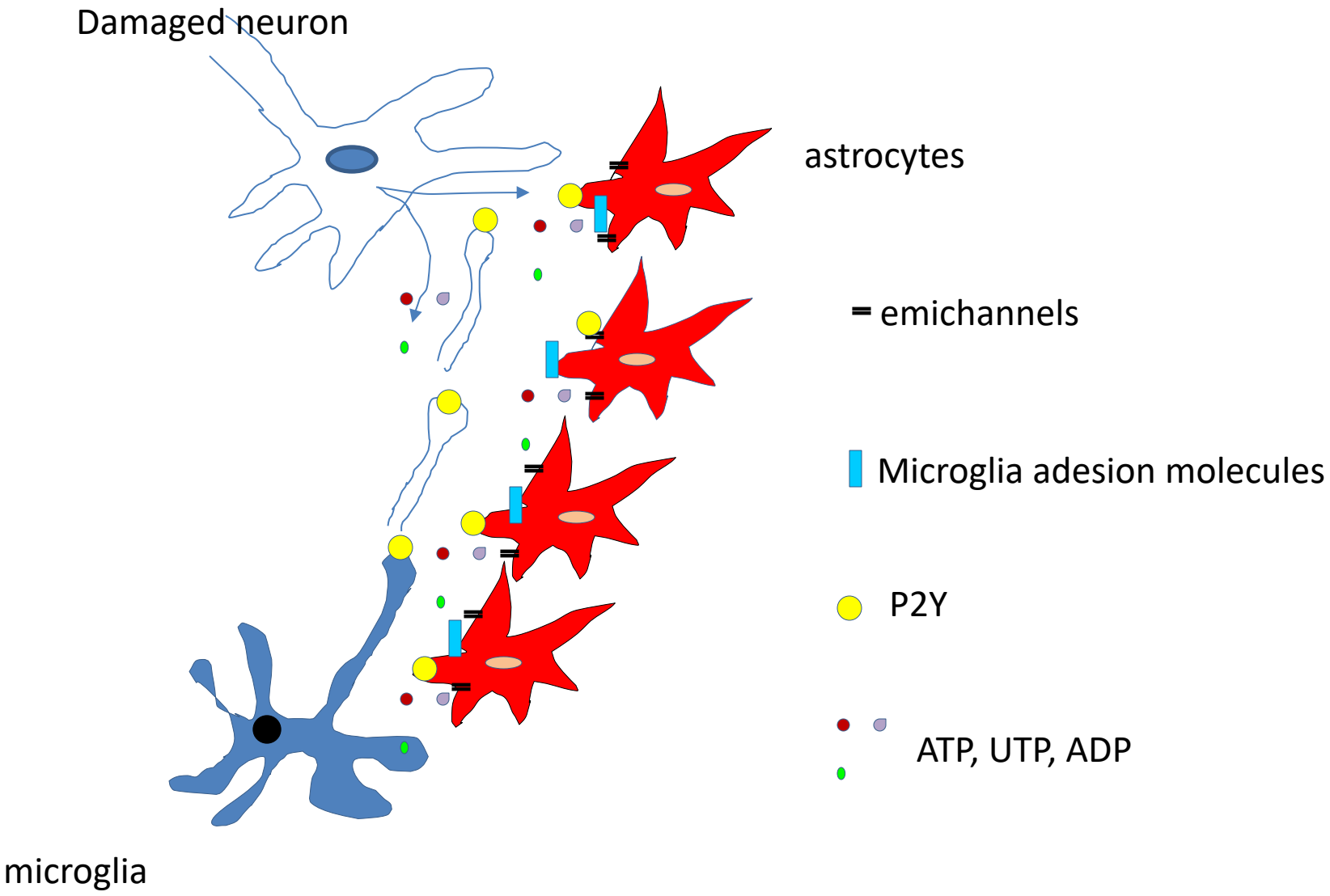




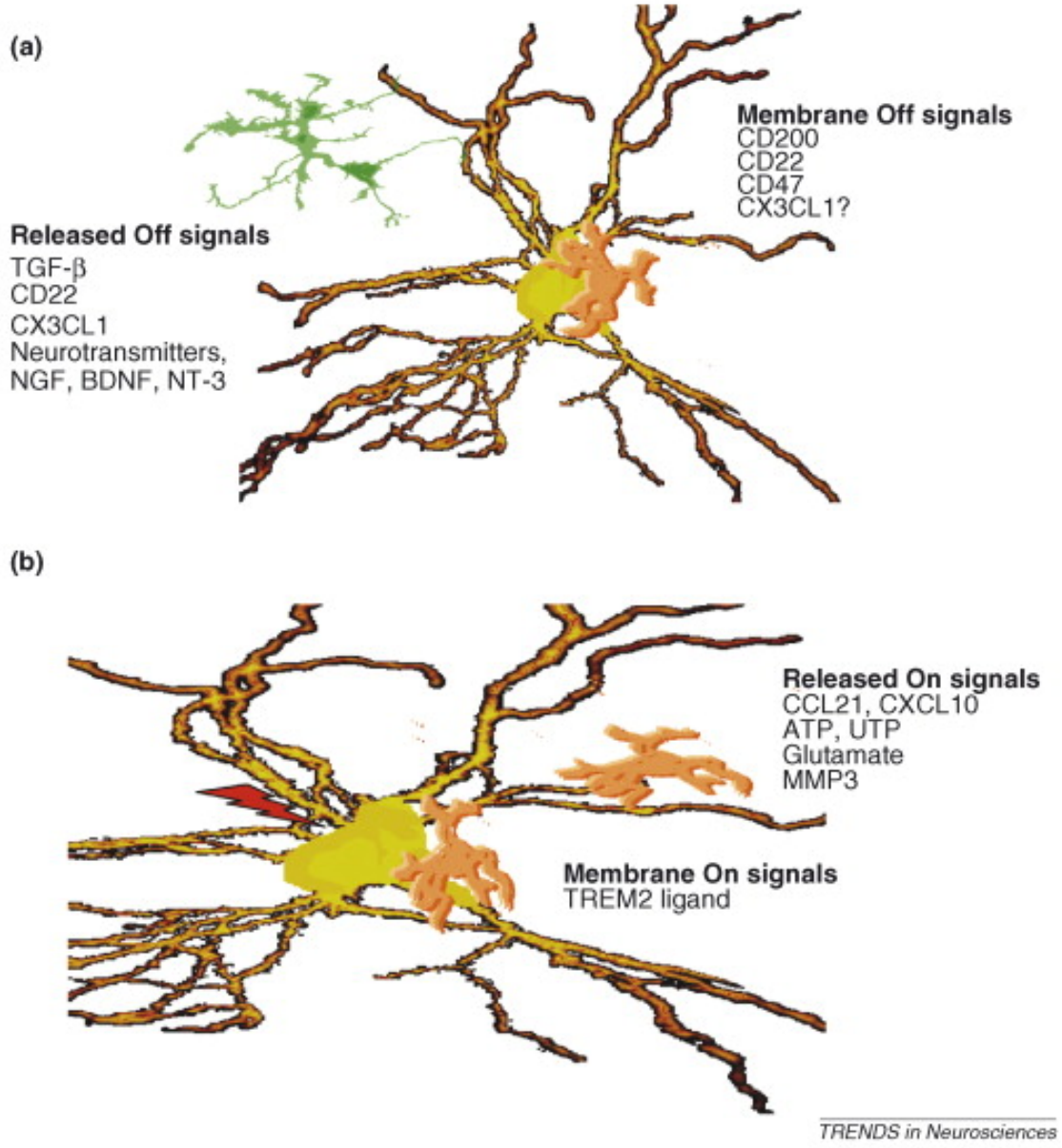
MICROGLIA

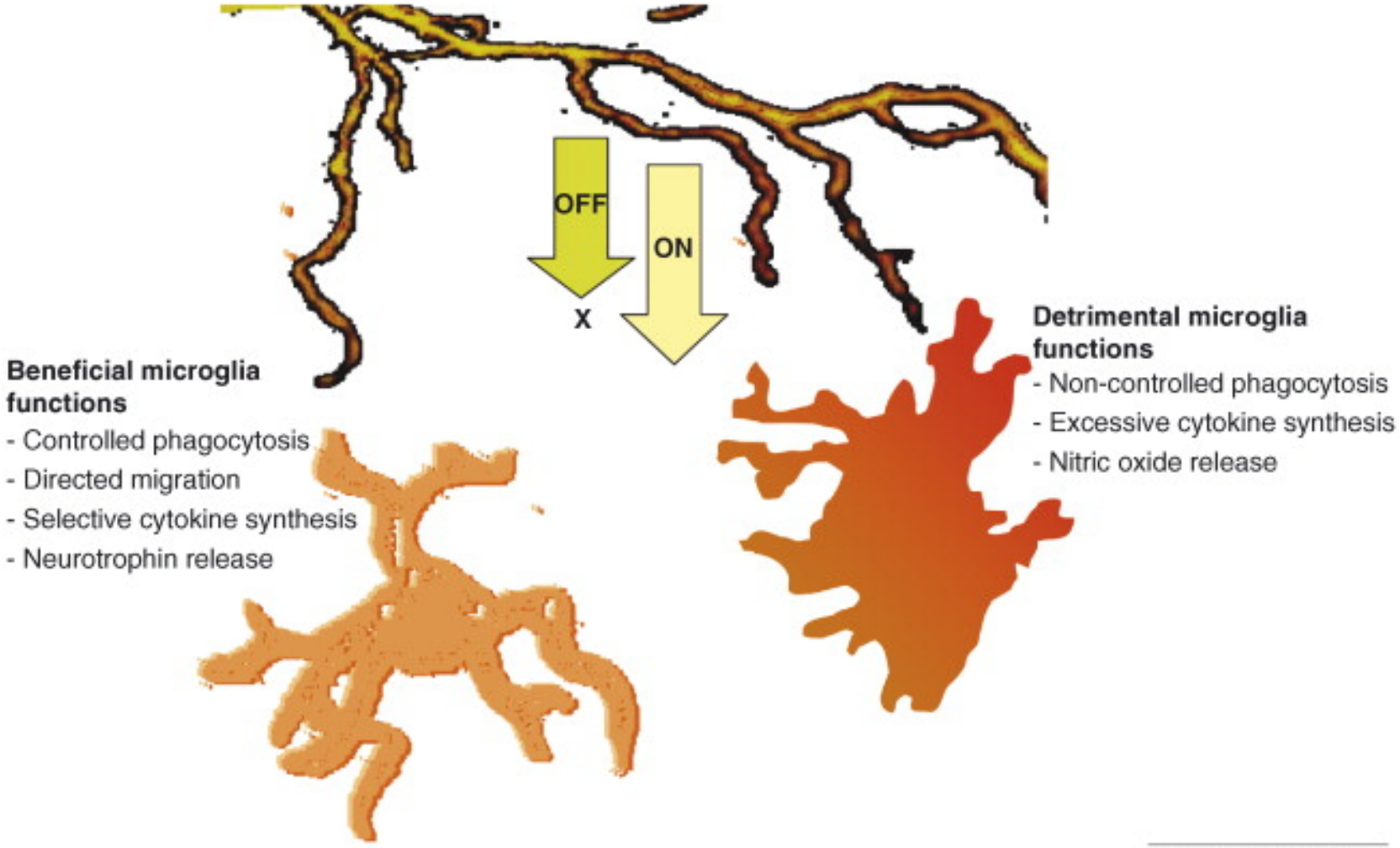


Microglial branch movement in normal and injured brain.



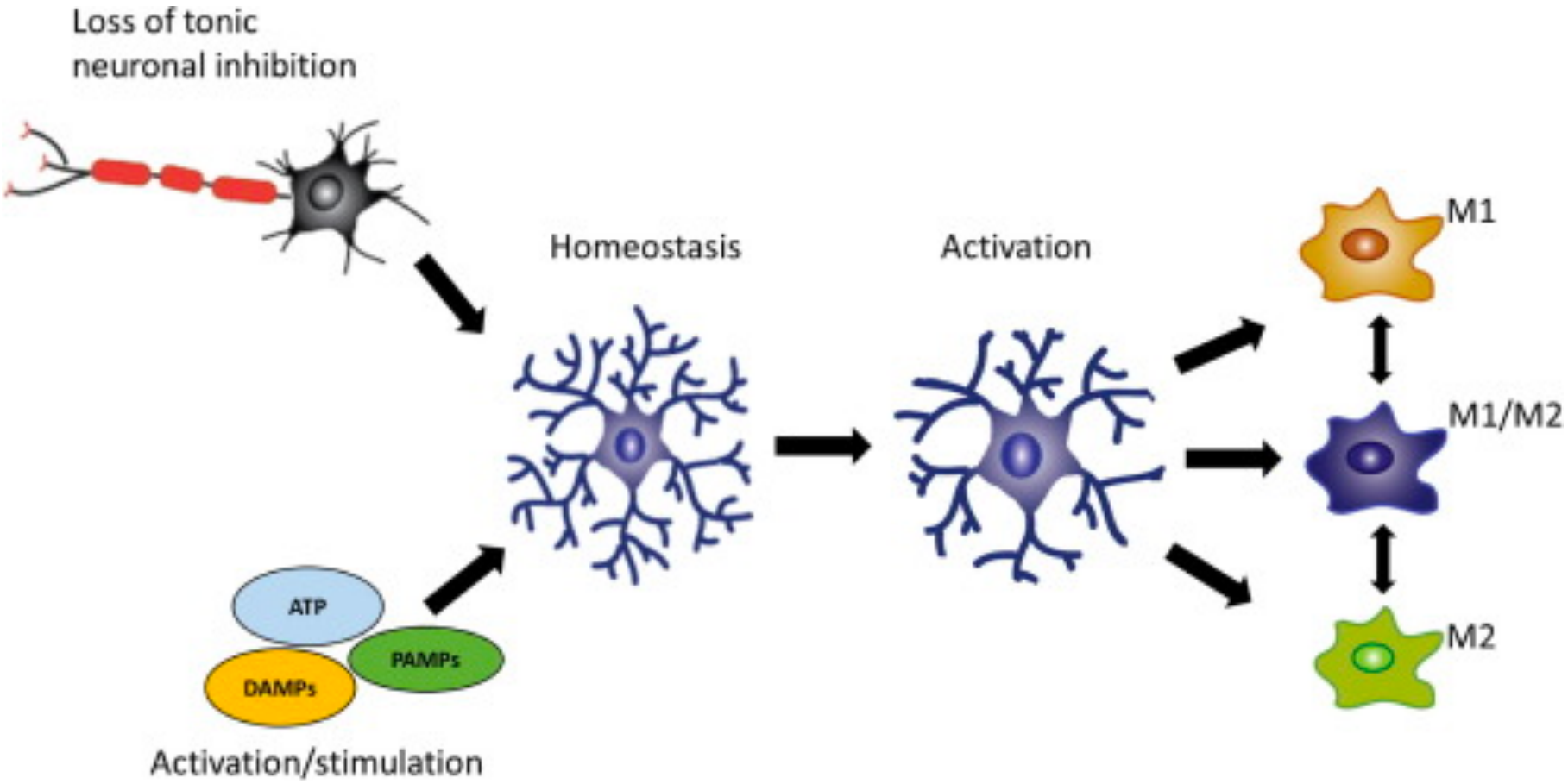
ON and OFF signals control microglia



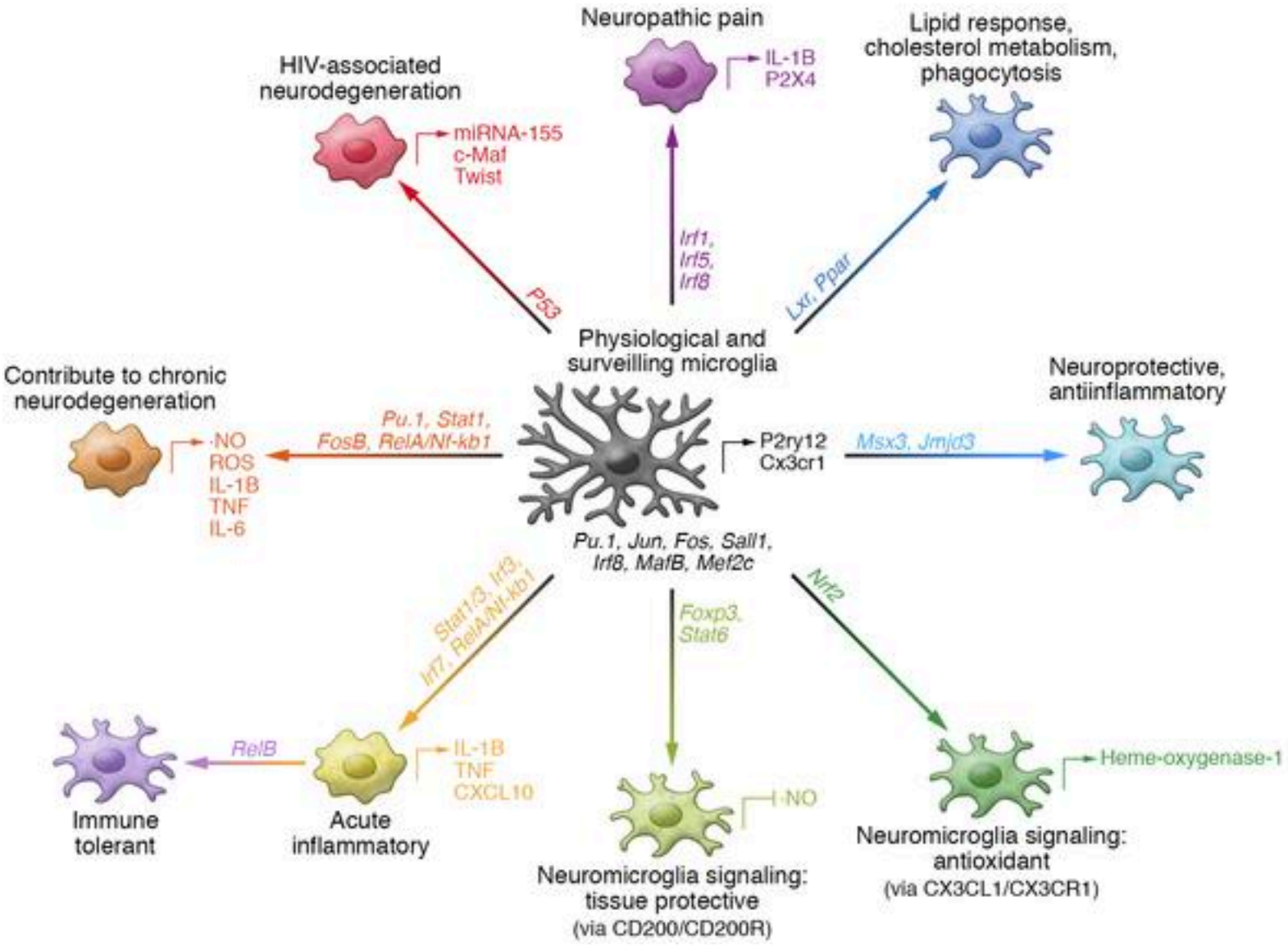


TRENDS in Neurosciences

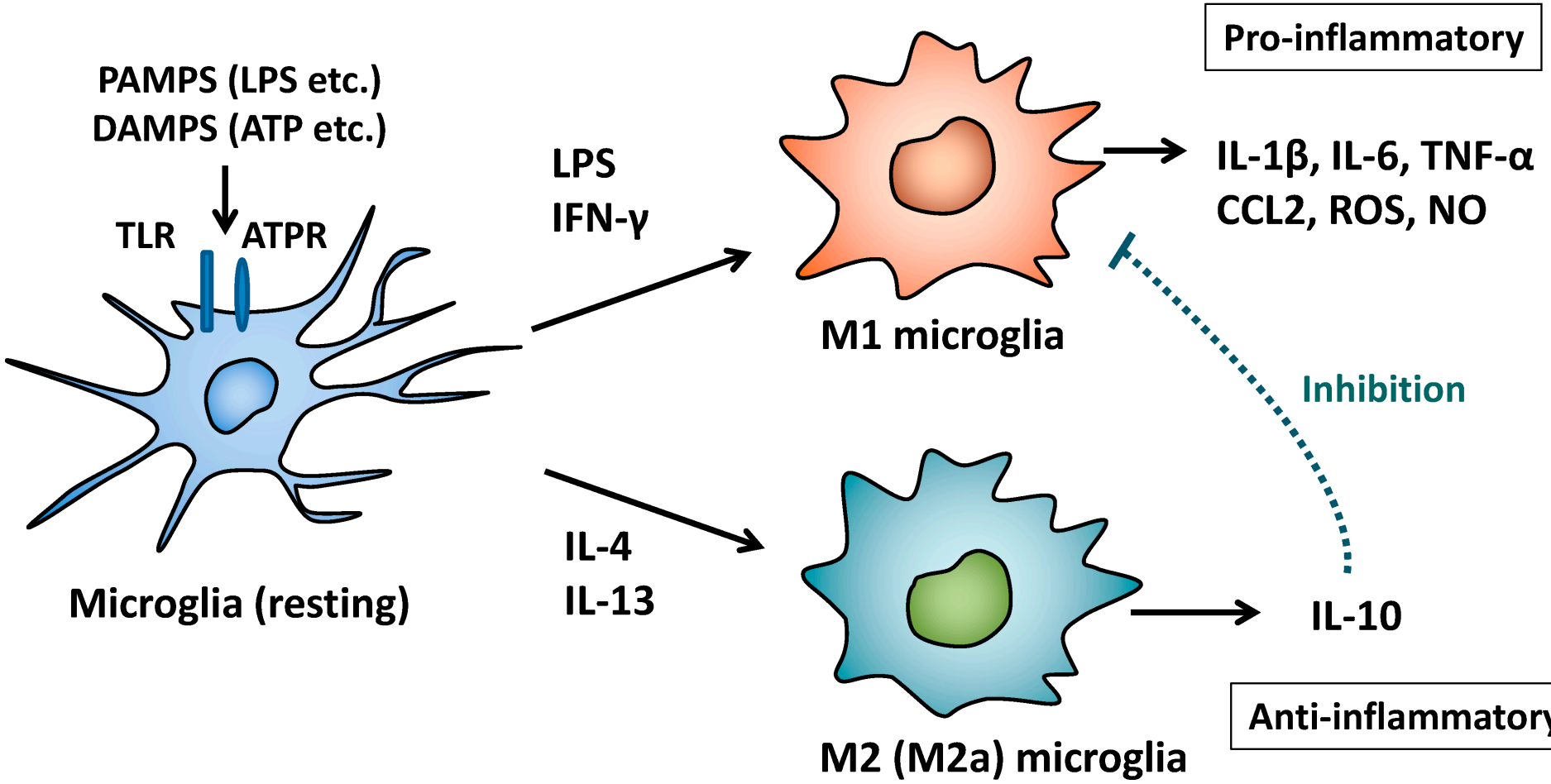
Microglia “activation”



Microglia phenotypes



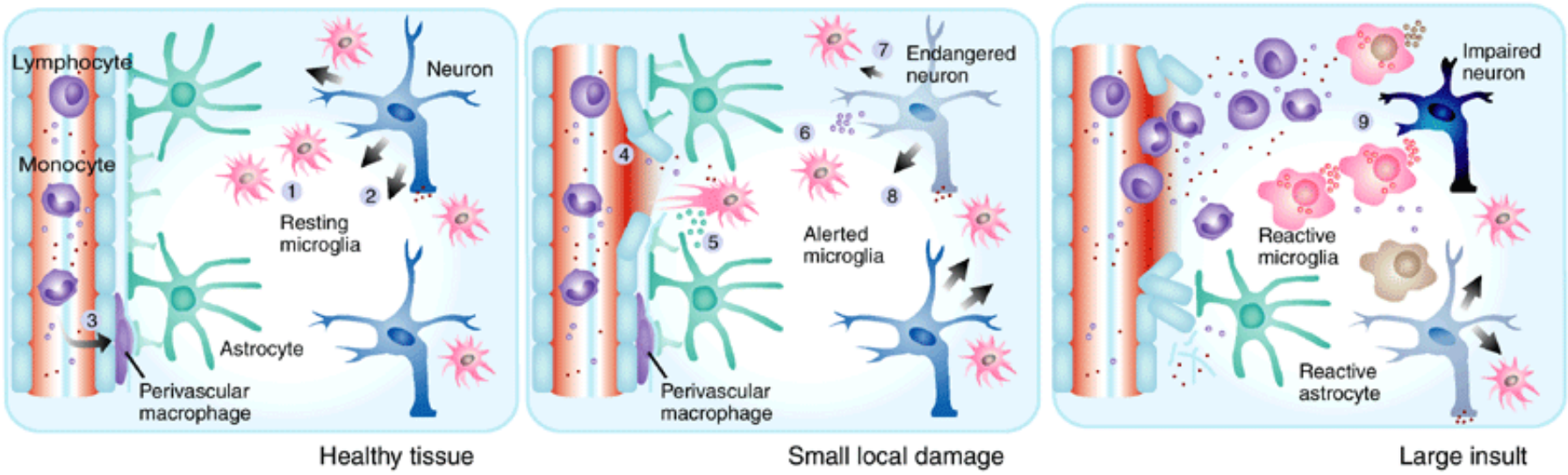
Microglia phenotypes



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

Fagocitosi microgliale

- Rimozione di tessuto danneggiato o non funzionante
    - Importante nello sviluppo
    - In patologie acute del SNC
    - Nella SM

Damage pattern of the entorhinal cortex

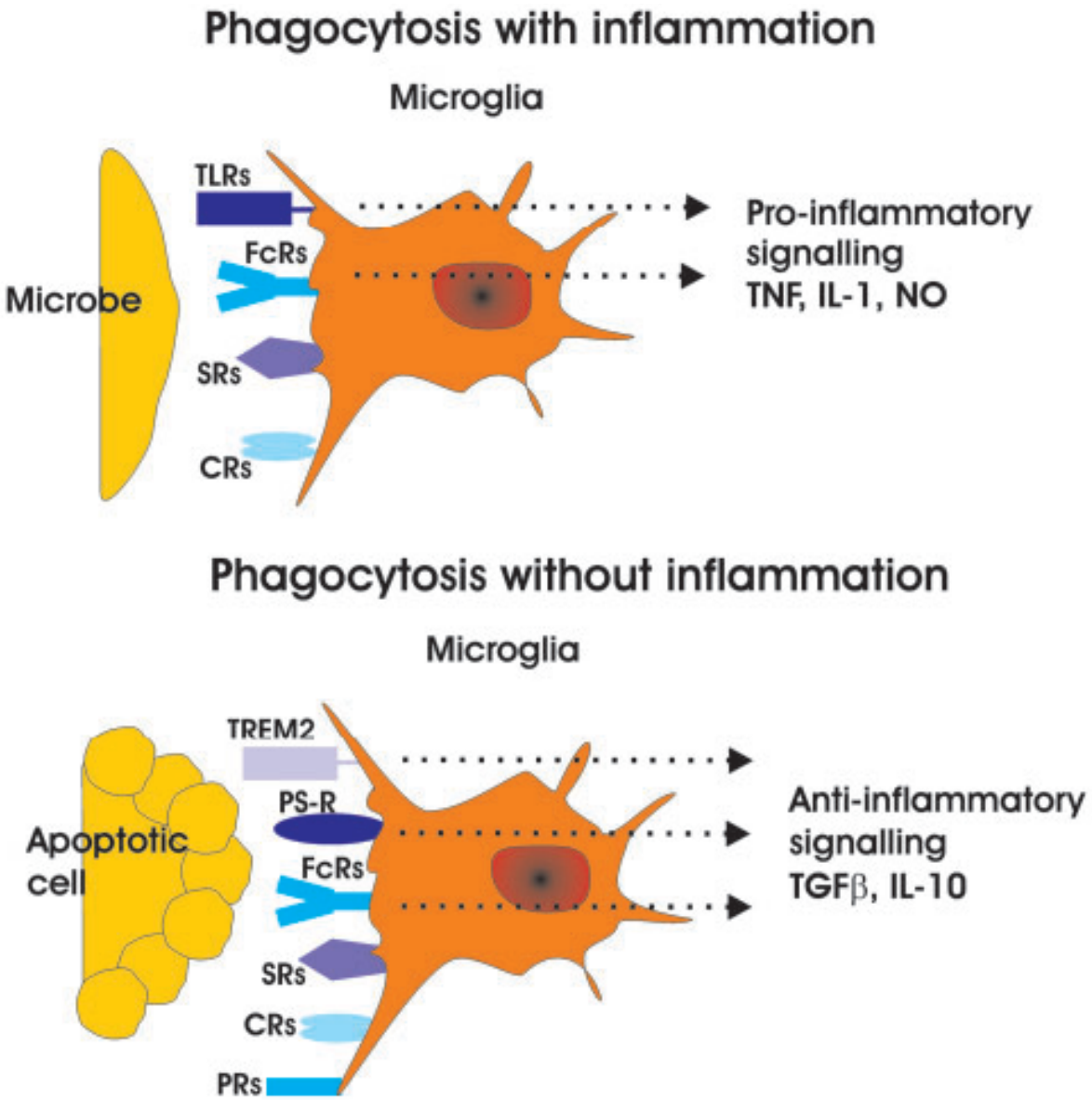
- Axonal damageMicroglial migration (3 d)
- Dendritic degeneration (8 d)
- MHC I-dependent process

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

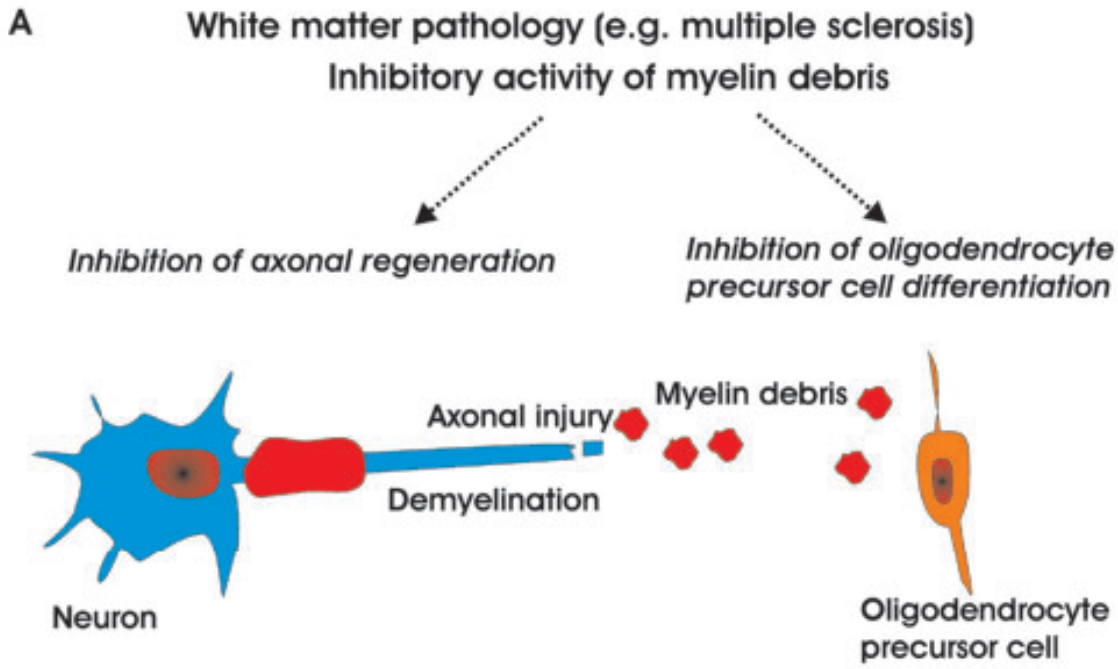
Receptors involved in µglia phagocytosis

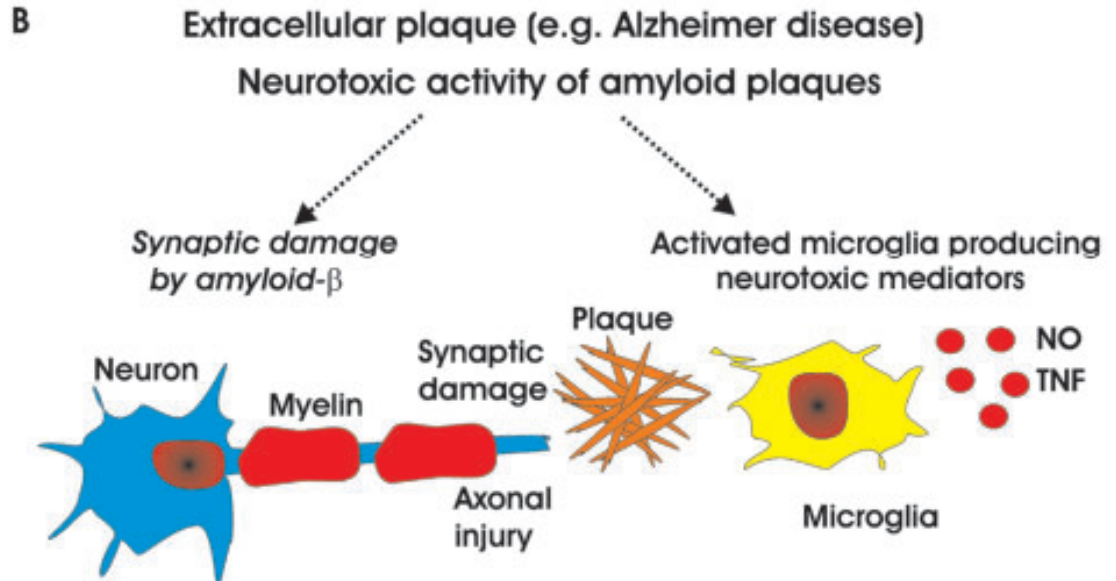


Multiple sclerosis

- 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).

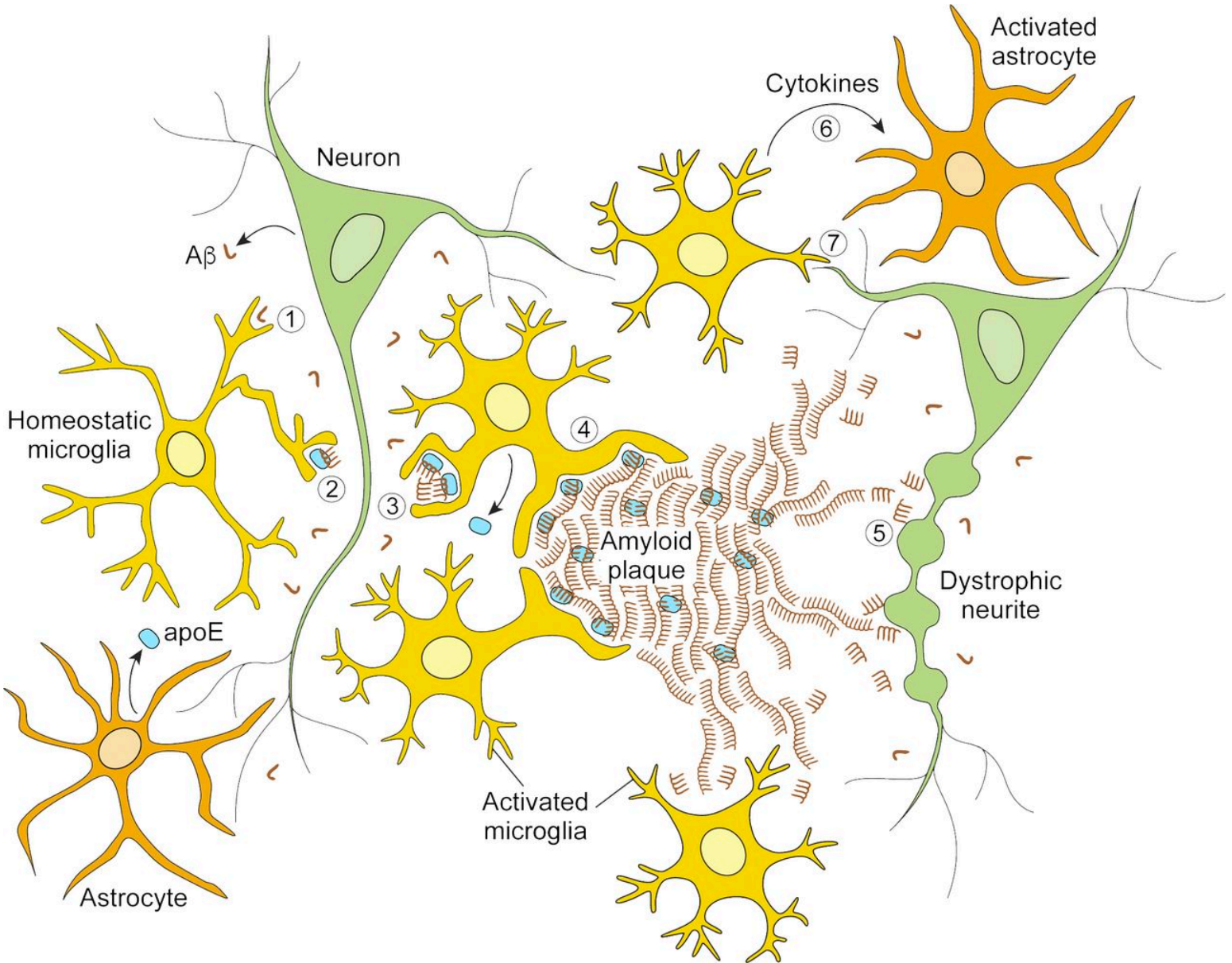
- Human genetics data point to a key role for microglia in the pathogenesis of AD. The majority of risk genes for AD are highly expressed (and many are selectively expressed) by microglia in the brain.

- 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.

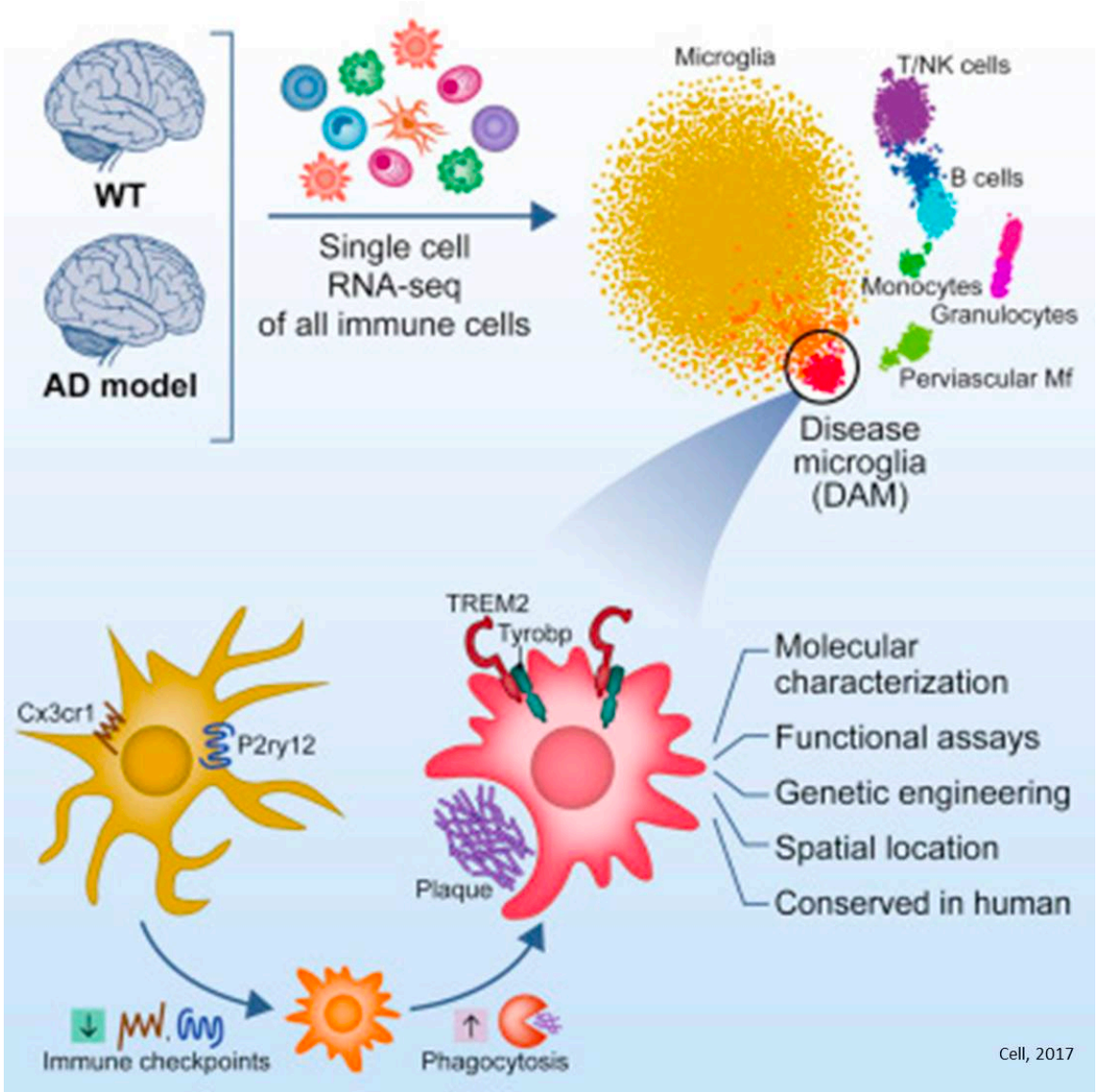
- On the other hand, there is also abundant evidence that activated microglia can be harmful to neurons. Microglia can mediate synapse loss by engulfment of synapses, likely via a complement-dependent mechanism; they can also exacerbate tau pathology and secrete inflammatory factors that can injure neurons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