

Biomedical Science

Molecular Genetics



HMG 44110A | Fall 2026-2027

Inherited Neurological Disorders

Glial Cells (Neuroglia) Neurobiology & Clinical Aspects

جميع الأوراق والمحتويات التابعة للمنصة محمية بموجب حقوق الملكية الفكرية. يُمنع منعاً باتاً نسخ، أو نشر، أو مشاركة أي محتوى أو مستندات تخص المنصة بأي شكل دون إذن مسبق. ويُعد أي تجاوز أو مخالفة لهذا القرار خرقاً قانونياً يعرض مرتكبه للمساءلة والملاحقة القانونية الفورية

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Nervous Tissue: Two Cell Types

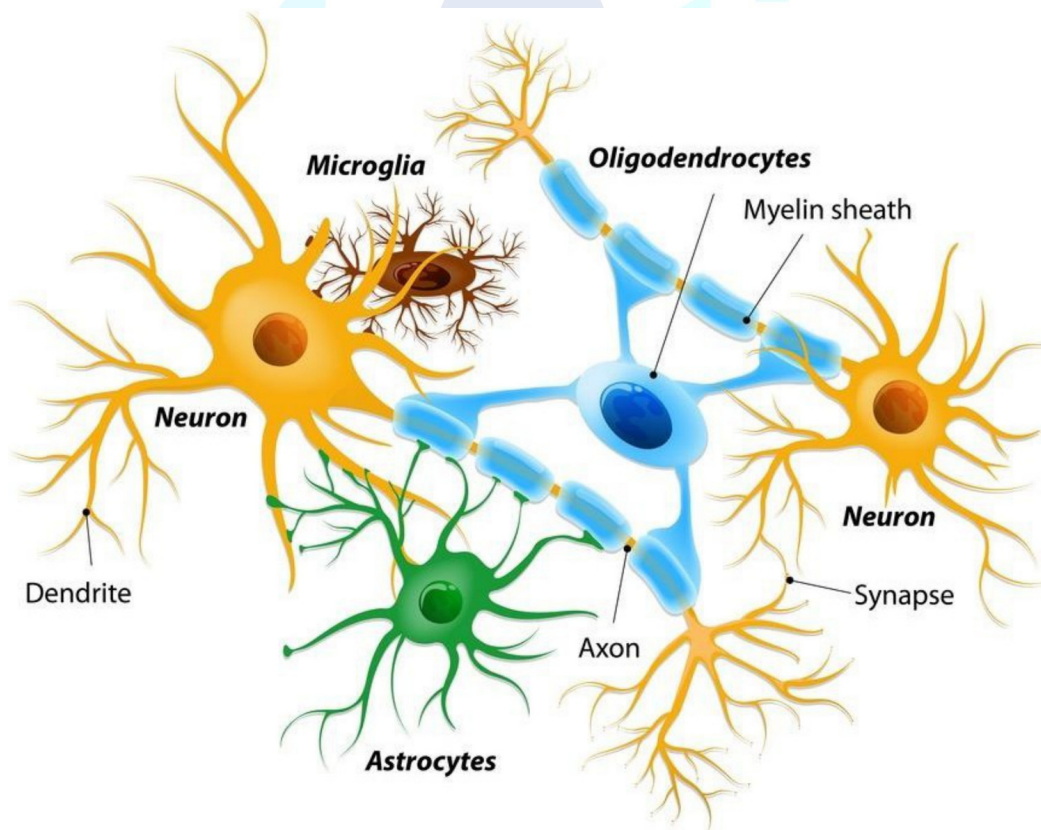
The Nervous tissue comprises **two** types of cells.

Neurons

- **Highly specialized cells.**
- Connect all regions of body to brain & spinal cord.
- Lost ability to undergo **mitosis**.

Neuroglia

- **Support, nourish, and protect neurons.**
- Much more in number than neurons.
- Continue to **divide throughout lifetime**.





Glia at a Glance

- 1 Neuroglia are **smaller** than neurons, and they are much **more numerous**.
- 2 In contrast to neurons, glia **do not generate or propagate nerve impulses**.
- 3 They can **multiply and divide** in the mature nervous system.
- 4 Brain tumors derived from glia, called **gliomas**.



Types of Neuroglia

THE NEUROGLIA IN THE CENTRAL NERVOUS SYSTEM (CNS)



Astrocytes



Oligodendrocytes



Microglial cells



Ependymal cells

THE NEUROGLIA IN THE PERIPHERAL NERVOUS SYSTEM (PNS)



Schwann Cells



Satellite Cells



Astrocytes

Astrocytes are **the most abundant glial cells** in the central nervous system (CNS).

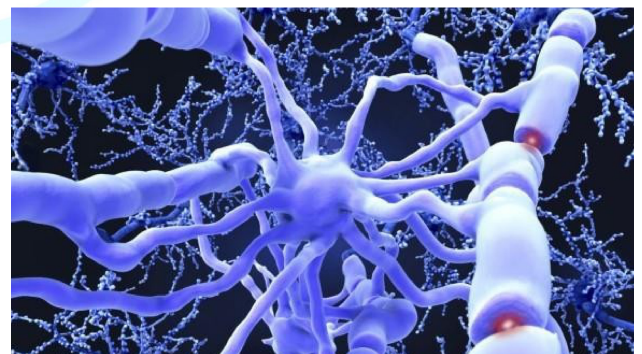
- Play a crucial role in **regulating** the **chemical environment around neurons**.
- Help **maintain ion balance**, control the **blood-brain barrier**, and provide **nutrients and structural support** to neurons.



Oligodendrocytes

Oligodendrocytes are found in the **CNS**.

- **Responsible for producing myelin**, a fatty substance that wraps around the axons of neurons.
- Myelin acts as an **insulator**, **increasing the speed and efficiency of nerve signal transmission**.





Microglia

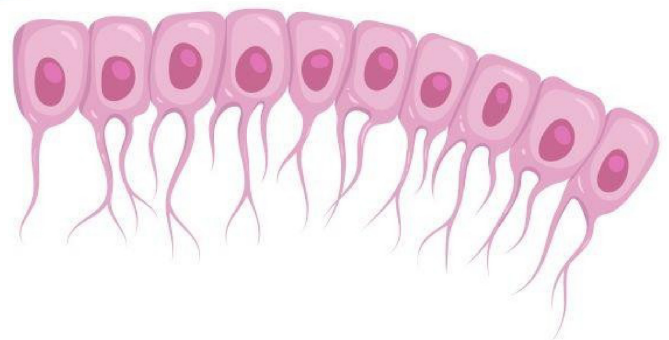
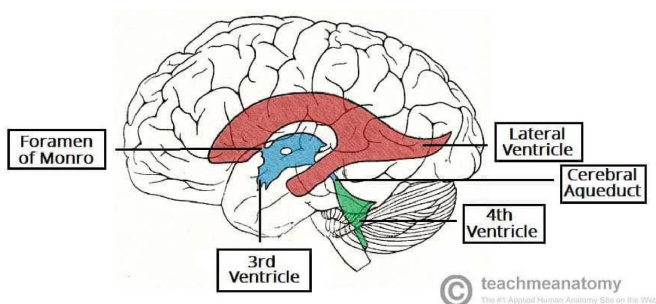
Microglia are the **immune cells** of the CNS.

- They function as **macrophages**, **phagocytosing dead cells, and pathogens**.
- Play a role in the **immune defense** and maintaining a **healthy environment in the brain and spinal cord**.



Ependymal Cells

Ependymal cells **line the ventricles of the brain and the central canal of the spinal cord**. They **produce cerebrospinal fluid (CSF)**, which surrounds and cushions the brain and spinal cord, providing **buoyancy and protection**.





Why Are We Studying It?

The most notable finding in neurodegenerative diseases is the **progressive death of neurons.**

However, **neuroglial changes can precede and facilitate neuronal loss.**

Astroglial malfunction

Astroglial cells maintain the brain homeostasis, and are responsible for **defense and regeneration**, so their malfunction may manifest as:

Damage or death of neurons **(neurodegeneration)**.



Weakness or lack of support for neurons.



Overactive astrocytes **(increased reactivity)**, which can worsen brain diseases.

Neuroglia may represent a **novel target for therapeutic intervention**, be that prevention, slowing progression of or possibly curing neurodegenerative diseases.



A Central Element of Neuropathology

The neuroglial cells are the **homeostatic and defensive arm of the nervous system**, which ensures proper organ internal environment associated with brain function.

Conceptually, neurological diseases can be defined as **homeostatic neuroglia failure**, often associated with the inability of homeostatic neuroglia to provide full neuroprotective support.

NEURAL CELLS RESPOND TO DAMAGE IN FUNDAMENTALLY DIFFERENT WAYS

Neurons

Become **stressed** and **lose their primary function** of transmitting and processing information.

Neuroglial cells

In contrast, they **actively respond** by increasing a defensive response, collectively known as **reactive gliosis**.

REACTIVE GLIOSIS

A **universal reaction to brain injury**. It involves **astrocyte hypertrophy** and **upregulation of glial fibrillary acidic protein (GFAP)**.

While reactive gliosis is well-documented, the **precise origin and long-term fate** of the responding glial cells remain unclear.



Neuroglia in Neurodegeneration

GLIOSIS

A **fibrous proliferation of glial cells** in injured areas of the CNS.

In many neurodegenerative processes, **atrophic and degenerative changes in astroglia precede astrogliosis**, likely triggered by early lesions or alterations in the neural environment — sometimes even **before the appearance of damaged or dying neurons**.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Astrodegeneration and astroglial atrophy occur **before clinical symptoms and neuronal death**.



Huntington's Disease (HD)

- A **decreased astroglial L-glutamate uptake** as well as an **aberrant release of L-glutamate from astrocytes** contributes to **neurotoxicity**.
- **Astroglial reactivity** also contributes to HD.
- Suppression of astroglial response by **inhibition of JAK/STAT3 signalling cascade** increases the number of huntingtin aggregates, thus **worsening pathological progression**.



Parkinson's Disease (PD)

Astrocytes are supposed to play a **neuroprotective role**.



Astrocytes contribute to the **metabolism of dopamine**; astrocytes were shown to **convert L-DOPA to dopamine**. In the striatum, astrocytes act as a **reservoir for L-DOPA**, which they release to be subsequently transported to neurons.



The level of **glial fibrillary acidic protein (GFAP)** expression is **decreased** in astrocytes in PD human tissue, indicating **astroglial atrophy** and reduced astroglial response, which may reflect **compromised astroglial neuroprotection**.



Oligodendrocytes in Neurodegeneration

Oligodendrocytes also undergo **degenerative changes** in the context of neurodegeneration.



The progression of AD, for example, is accompanied by **substantial shrinkage of the white matter**.



Degenerative changes are also observed in **oligodendroglial precursors / NG2 glial cells** that may reflect a **reduction in their remyelinating capacity**.



Astrocytes in Alzheimer's Disease

- The **pathological potential of astroglia** in the context of dementia was realized by **Alois Alzheimer**, who often observed **activated glial cells in close contact with pathologically altered neurons**.
- He also described glia as a **cellular component of the senile plaque**.
- Subsequent studies frequently mentioned **astroglial reactivity** in the context of AD, although detailed analysis of astroglial pathology started to be investigated **only very recently**.



Astrodegeneration

Atrophic astrocytes fail to provide adequate homeostatic support, thus further **worsening neuronal function**.

These changes may, therefore, account for the **early cognitive impairment**, which results from **loss and weakening of synapses**, rather than from neuronal death.

Astrodegenerative changes may contribute to the development of **early AD pathology**.



Astroglial Reactivity

Astrocytes become **reactive** in response to **injury and inflammation**.

AT LEAST TWO DISTINCT CATEGORIES OF REACTIVE ASTROCYTES



**Hypertrophic
reactive astrocytes**



**Scar-forming
astrocytes**

FOUND IN MANY NEUROLOGICAL DISEASES, SUCH AS

Alzheimer's disease (AD)

**Amyotrophic lateral sclerosis
(ALS)**

Multiple sclerosis (MS)

Epilepsy

Stroke

Traumatic brain injury (TBI)

MARKER

Upregulation of **glial fibrillary acidic protein (GFAP)** is widely used as a **marker of reactive astrocytes**.

Reactive astrocytes show **hypertrophy with thicker processes**.



Glial Scar Formation

Roles of reactive astrocytes can be **neuroprotective** or **neurotoxic**, **depending on the context.**

Reactive astrocytes **form in response to brain or spinal cord injury.**

These astrocytes undergo **morphological and functional changes.**

AT THE INJURY SITE, THEY FORM GLIAL SCARS THAT...

INITIALLY

Protect the CNS by **sealing the damage** and **containing inflammation.**

BUT MAY LATER

Inhibit axonal regeneration and impede recovery.



Calcium Signalling & Reactivity

Astrocyte reactivity is a **key component of the CNS defensive response** to various neuropathological insults.



The molecular mechanisms that initiate astrogliosis are **still not fully understood**.

Emerging evidence highlights the **critical role of cytosolic calcium (Ca²⁺) signaling**, particularly Ca²⁺ release from the **endoplasmic reticulum (ER)**.



The **type II inositol 1,4,5-trisphosphate receptor (InsP₃R2)** is a major ER Ca²⁺ release channel in astrocytes.



Genetic Deletion of InsP₃R2

GENETIC DELETION OF INSP₃R2 IN ASTROCYTES

Leads to a **significant reduction in astroglial reactivity** following CNS injury.



Demonstrates the **dependence of reactive gliosis on ER-mediated Ca²⁺ dynamics**.



Aberrant Ca²⁺ Signals in AD

Astrocytes are **highly sensitive to CNS injury or hyperexcitability**, and they rapidly respond by generating **intracellular Ca²⁺ signals**.

In pathological conditions, **aberrant Ca²⁺ signaling** is commonly observed in astrocytes particularly **near sites of tissue damage**.

Most evident in **hypertrophic (reactive) astrocytes**.

EVIDENCE FROM EXPERIMENTAL MODELS

Drug-induced seizure model

Astrocytes show a **rapid rise in Ca²⁺ levels** in response to **hyperexcitability**.

In vivo familial AD mouse model

Reactive astrocytes near **amyloid plaques** exhibit **frequent Ca²⁺ signals** and **calcium waves that originate from the plaques**.



Vesicular Trafficking in Astrocytes

Signs of **astroglial activation** are observed **before β -amyloid plaque formation**, suggesting early involvement of astrocytes in Alzheimer's pathology.

- 1 Astrocytes **store gliosignalling molecules** (e.g., ATP, glutamate, cytokines) in **membrane-bound vesicles**.
- 2 These molecules are released via **exocytosis**, a process triggered by **external stimuli and calcium influx**.
- 3 Vesicles are trafficked from the **Golgi complex** (deep in the cytoplasm) to the **plasma membrane** for secretion.

Golgi complex



Vesicle trafficking



Plasma membrane



Exocytosis

CALCIUM CONTROL

Vesicle trafficking is regulated by **increases in intracellular Ca^{2+} levels ($[\text{Ca}^{2+}]_i$)**, which serve as key signals in exocytotic release. This traffic is maintained by an **elaborate system regulated by increases in $[\text{Ca}^{2+}]_i$** .

3xTg-AD mice

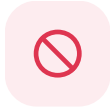
- Even **before cognitive symptoms** of Alzheimer's disease develop, astrocytes already show **disrupted vesicle trafficking**, suggesting that **cellular dysfunction precedes clinical manifestation**.
- Astrocytes isolated in the **pre-symptomatic phase** of the disease exhibit **alterations in vesicle traffic**.



Oligodendroglia in Disease

Central myelination is provided by oligodendrocytes in **white and grey matter**.

OLIGODENDROCYTE DEGENERATION AND DEATH LEADS TO



**Decreased
CNS myelination**



**White matter
shrinkage**

This pattern — **oligodendrocyte death + myelin loss + white matter shrinkage** — is a **universal feature** of brain and spinal cord diseases:

Stroke

Perinatal ischemia

Multiple sclerosis

Psychiatric disorders

Traumatic injury

AD

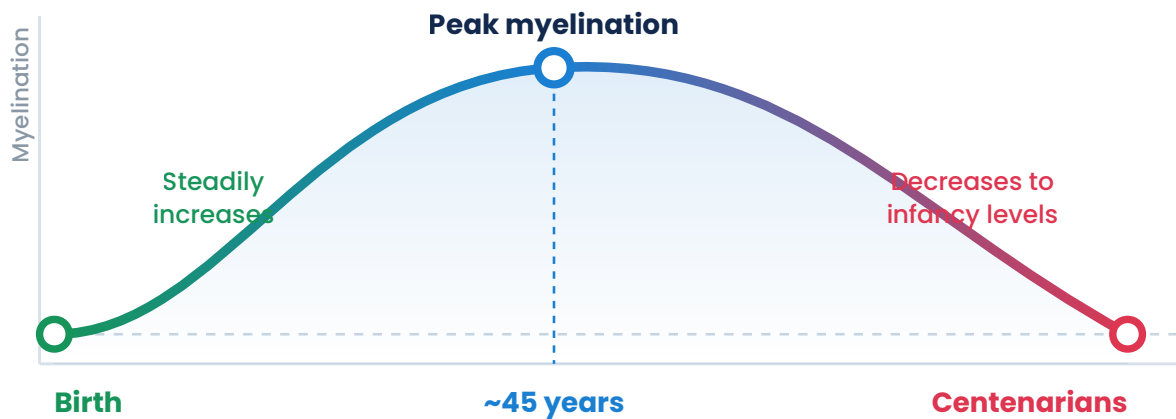
AGING

Myelin loss is a **characteristic feature of aging**. CNS decreased myelination occurs in **cognitive areas**: cerebral cortex — **frontal lobes (cognition and memory)**.



Myelination Across the Lifespan

Myelination follows a **lifespan curve**.



Steadily increases during postnatal development.

Peaks at around **45 years**.

Decreases in centenarians to infancy levels.

AGE-DEPENDENT MYELIN DETERIORATION — RHESUS MONKEYS

- **Primary visual cortices** affected.
- It appeared that there was **decreased paranode length in aging** — indicates **demyelination problems**.

These changes in the myelin developed **in parallel with the decrease in the self-renewal capacity** of oligodendroglial precursors / NG2 cells (**oligodendrocyte precursor cells, OPCs**).



Ca²⁺ Homeostasis in Oligodendroglia

Oligodendroglial cell death and myelin loss are linked to **abnormal calcium (Ca²⁺) homeostasis and signaling.**

THIS DYSREGULATION MAY ARISE FROM

Extracellular factors

Such as **neurotransmitter dyshomeostasis.**

Cellular factors

Including alterations in **Ca²⁺ regulatory mechanisms** — e.g. **channels, pumps, and transporters.**

IONOTROPIC RECEPTORS

Oligodendrocytes express **multiple ionotropic receptors**, including:

L-glutamate receptors

P2X purinergic receptors

These receptors are **permeable to Ca²⁺**, allowing **calcium influx when activated.**



Ca²⁺ Overload & Cell Death

Excessive or prolonged activation of these receptors can cause:

Cytosolic Ca²⁺ overload



Mitochondrial Ca²⁺ accumulation



Increased production of **reactive oxygen species (ROS)**



Release of **pro-apoptotic factors**



Together, these changes trigger **oligodendrocyte apoptosis** and **myelin damage**.

EXCITOTOXICITY

Especially from **L-glutamate** and **ATP**, may further contribute to **oligodendroglial cell death in AD**.



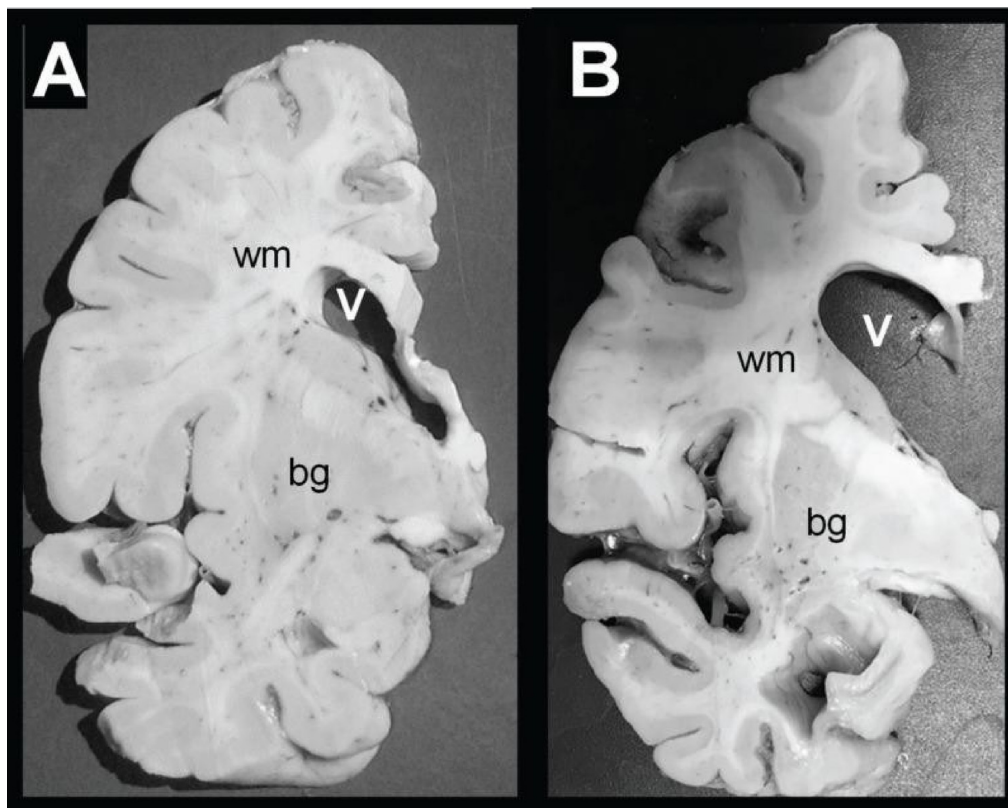
White Matter in Alzheimer's Disease

White matter

Shows **signs of degeneration**.

Oligodendrocytes

The number is **significantly reduced**, reflecting **progressive myelin and glial loss**.



White matter atrophy in AD. Postmortem coronal slices of the left cerebral hemisphere from patients with **(A)** normal aging or **(B)** advanced AD. Panels A and B show approximately the same coronal slice levels depicting the cingulate gyrus, corpus callosum, basal ganglia (bg), central and periventricular posterior frontal white matter (wm) and lateral ventricle. Note the markedly atrophic white matter and associated ex vacuo enlargement of ventricles (V) in (B) AD relative to (A) control.

de la Monte SM, Grammas P. Insulin Resistance and Oligodendrocyte/Microvascular Endothelial Cell Dysfunction as Mediators of White Matter Degeneration in Alzheimer's Disease. In: Wisniewski T, editor. Alzheimer's Disease [Internet]. Brisbane (AU): Codon Publications; 2019 Dec 20. Figure 1. doi: 10.15586/alzheimersdisease.2019.ch8



Early Biomarkers & NG2 Glia

NG2 glia, also called **oligodendrocyte precursor cells (OPCs)**, are involved in **myelin repair and plasticity**.

- Myelin and oligodendrocyte abnormalities in Alzheimer's disease occur **before the onset of clinical symptoms**, making them potential **early biomarkers of the disease**.
- **White matter lesions** are particularly prominent in the **early stages of AD**, especially in **periventricular and deep white matter** regions.

NG2 GLIA IN 3XTG-AD MICE

Early stages

Significant **morphological atrophy** and a **decrease in NG2 glia** are observed.

Later stages

NG2 glia become **associated with senile plaques**, extending their processes into the plaques.

A similar **reduction in NG2-positive profiles** has also been observed in **human AD post-mortem tissue**.



Remodelling of the Connectome

All these alterations in **myelin, oligodendrocytes, and NG2 glial cells** may lead to **pathological remodeling of the brain's connectome.**

THIS INCLUDES



**Disrupted
axonal conduction**



**Disintegration of
white matter tracts**

1

**Myelin, oligodendrocyte
& NG2 alterations**

2

**Pathological remodelling
of the connectome**

3

**Impaired neuronal
communication**

4

**Cognitive decline
in Alzheimer's disease**

Together, these changes **impair neuronal communication** and ultimately contribute to **cognitive decline in Alzheimer's disease.**



Microglia in Alzheimer's Disease

- Microglial alterations — **both reactive and degenerative** — play a **critical role in the progression of AD.**
- **Reactive microglia**, along with astrocytes, are frequently found **clustered around senile plaques** (amyloid plaques).
- These activated microglia release **proinflammatory cytokines, chemokines, and other mediators** that may contribute to **neuronal injury and disease progression.**



Loss of Microglial Function

Despite their activation, **loss of essential microglial functions** has also been reported in AD.

IN APP/PS1 TRANSGENIC MOUSE MODELS, THE EMERGENCE OF AMYLOID PLAQUES IS ASSOCIATED WITH

A decline in **microglial phagocytic capacity**,



Leading to **impaired clearance of β -amyloid**,



Ultimately facilitating **plaque accumulation and neurotoxicity.**



Microglial Degeneration in Aging

- **Microglial degeneration in aging brains** may increase **vulnerability to Alzheimer's pathology**.
- In particular, the ageing process can **impair microglial surveillance**, weakening the brain's **innate immune defense**.
- **β -amyloid ($A\beta$)** — whether in its **soluble, oligomeric, or fibrillar** forms — is a **potent activator of microglia**.

IN VIVO IMAGING — TRANSGENIC MOUSE MODELS (E.G. APP/PS1)

- Microglia are **recruited to $A\beta$ plaques**, but...
- This activation occurs **after plaques have already formed**, indicating that microglia respond **reactively rather than preventively**.



Phenotype Shift During AD

EARLY IN DISEASE

Microglia may attempt **protective roles** like **phagocytosing $A\beta$** .

AS DISEASE ADVANCES

Microglia may become **dystrophic or dysfunctional**, losing clearance abilities and contributing to **chronic inflammation**.



In Conclusion

Pathological changes in neuroglia, including but not restricted to **astrocytes, oligodendrocytes, NG2 cells and microglia**, are **omnipresent in neurodegenerative diseases**.



These neuroglial changes include **cellular degeneration and asthenic responses** at **earlier stages** of a disease, and, as disease progresses, evident by occurring neuronal damages, **neuroglia turns to reactive phenotypes**.

The specific **morphofunctional changes in glia** not only occur during **distinct temporal domains**, but also are **region-specific**.

Since the **changes in neuroglia precede those in neurons**, it is likely that the neuroglial cells failure to maintain CNS homeostasis is a **malefactor causative to neuronal death**.

Neuroglia therefore may represent an **opportunistic target for therapeutic intervention** directed towards **prevention and conceivably curing** neurodegenerative diseases.



To Summarise...

TYPES

4 + 2

The neuroglial family

- CNS: astrocytes, oligodendrocytes, microglial cells, ependymal cells
- PNS: Schwann cells and satellite cells
- Support, nourish and protect neurons; divide throughout lifetime

ASTROCYTES

GFAP

Most abundant glial cell

- Regulate the chemical environment around neurons
- Maintain ion balance and control the blood-brain barrier
- GFAP upregulation is the marker of reactive astrocytes

OLIGODENDROCYTES

~45 yr

Myelin peaks, then falls

- Produce myelin that insulates axons and speeds transmission
- Myelination peaks at around 45 years of age
- Decreases in centenarians to infancy levels

MICROGLIA

A β

Immune cells of the CNS

- Function as macrophages, phagocytosing dead cells and pathogens
- Cluster around senile plaques and release proinflammatory cytokines
- Recruited only after plaques have already formed

CALCIUM

InsP₃R2

Ca²⁺ drives reactivity

- Major ER Ca²⁺ release channel in astrocytes
- Its deletion reduces astroglial reactivity after CNS injury
- Ca²⁺ overload triggers oligodendrocyte apoptosis

TIMING

Early

Glia change before neurons

- Astroglial atrophy precedes astrogliosis and neuronal death
- Myelin abnormalities are potential early biomarkers of AD
- Neuroglia may be a target for therapeutic intervention

THE CORE ARGUMENT

Homeostatic neuroglia



Degeneration & asthenic response



Reactive phenotypes



Neuronal death