General Pathophysiology of Neuroglia

Neuroprotection and neurotoxicity: astroglial dichotomy

Verkhratsky, Sofroniew, Messing, deLanerolle, Rempe, Rodriguez, Nedergaard M (2012) ASN neuro 4, e00082

Reactive astrogliosis

All types of brain insults, regardless of aetiology, trigger a complex astroglial response, which is manifested by astrocyte hypertrophy and proliferation. This glial response is defined as reactive astrogliosis.

Reactive astrogliosis is a defensive brain reaction which is aimed at

(i) isolation of the damaged area from the rest of the CNS tissue;
(ii) participation in the neuroinflammatory response;
(iii) reconstruction of the blood–brain barrier; and
(iv) facilitation of the remodelling of brain circuits in areas surrounding (v) the lesioned region.

Reactive astrocytes in a model of post-traumatic epilepsy induced by cortical injection of a ferrous chloride solution

Verkhratsky, Sofroniew, Messing, deLanerolle, Rempe, Rodríguez, Nedergaard M (2012) ASN Neuro 4, e00082

Initiation and regulation of reactive astrogliosis


Glial reactivity and gliodegeneration

Gliodegeneration

Gliopathology in major neurological conditions and diseases

Astroglia in neurological diseases

Alexander's disease – primary genetic astrogliopathology

The disease is caused by mis-sense mutations of the GFAP gene; these aberrant genes are absent in parents, and therefore represent de-novo dominant GFAP gene mutations.

Histological hallmarks:
(i) Accumulation of Rosenthal fibres in astrocytes
(ii) Enlarged astrocytes.

MRI of the patient at 7 years showing cystic degeneration in the frontal lobes, enlarged ventricles and some atrophy of the vermis

Rosenthal fibers appear as dark nuggets in astrocytic endfeet surrounding blood vessels (asterisks).


Astroglia in neurological diseases

Alexander’s disease – primary genetic astrogliopathy

Wild Type

Figure 7. Assembly patterns of wild type and mutant GFAP in transfected cells. SWvim- cells were transfected with the indicated GFAP expression vectors and immunostained for GFAP 2 days later. Wild type and V115I GFAP form normal appearing filament networks, whereas K63Q and A253G form ring-like aggregates and E210K forms needle-like aggregates. Images for wild type, K63Q and E210K are reprinted with permission from Li et al., 2005; copyright by Wiley-Liss, Inc.

Astroglia in neurological diseases

Ischaemia and stroke

The disruption of blood flow in the brain can be caused either by blood vessel rupture, which results in haemorrhage, or by a restriction of blood supply to the brain or parts of the brain, commonly referred to as brain ischaemia, due to vascular occlusion (because of thrombosis or embolism), or to a systemic decrease in blood supply (for example, associated with heart failure). As a consequence, brain ischaemia can be either global, or focal, the latter corresponding to a stroke.

Astroglia protect the brain against ischaemia

Spatial and temporal progression of stroke

Possible outcomes:
- Recovery
- Cells survive but malfunction
- Selective cell death

Astrocytes may exacerbate brain damage upon ischaemia and contribute to infarct expansion.

Brain oedema

Cytotoxic oedema

Excess of extracellular K⁺/glutamate

Collapse of extracellular space

Brain oedema: consequences

Collapse of extracellular space
Reduced volume of the synaptic cleft
Compromised uptake of K⁺ and glutamate
All promote depolarisation and excitotoxicity

Hepatic Encephalopathy: A Primary Astrogliopathy

Hepatic encephalopathy results from liver failure and subsequent increase in the concentration of ammonia in the blood and in the cerebrospinal fluid.

Exposure of cortical astrocytes to ammonia results in a wide range of molecular and functional changes including cell swelling, decreased glutamate uptake, increased glutamate release, altered glycine transport, altered expression of the glucose transporter GLUT-1, reduced expression of the structural protein GFAP as well as oxidative and nitrosative stress.

This leads to a rapidly progressing failure of astroglial function, brain oedema, failure of brain ion, neurotransmitter and metabolic homeostasis, excitotoxicity and death.

Astroglia in neurological diseases

Astroglia in neuropsychiatric disorders

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Pathological potential of oligodendroglia

Neuropathology of oligodendroglia

Wallerian degeneration in CNS

Neuropathology of oligodendroglia

Wallerian degeneration in CNS
Neuropathology of oligodendroglia

Oligodendrocytes and oligodendroglial precursors are highly vulnerable to excitotoxicity and ischaemic insults


Periventricular leukomalacia (PVL) is the predominant form of brain injury and the leading known cause of cerebral palsy and cognitive deficits in premature infants.


Periventricular leukomalacia results from hypoxic damage to the white matter; the primary target is represented by oligodendroglial precursors and oligodendrocytes. Massive death of oligodendroglial cells initiates activation of microglia and secondary neuroinflammation.


Multiple sclerosis: Oligodendrodegeneration and demyelination

Multiple sclerosis (MS) was recognized by the mid 19th century, and already in 1871 Hammond referred to it as a cerebrospinal sclerosis; it was Charcot who, in 1877, realized the role of disrupted myelin sheath in the pathogenesis of this disease. MS is an inflammatory demyelinating disease of the CNS, which culminates in progressive neurological deterioration. The etiology of MS remains elusive, as both genetic predisposition and environmental factors are indicated. The importance of genetic predisposition is evident from very high concordance of the disease occurrence between monozygotic twins, whereas the environmental factors are implicated by the existence of geographical areas with remarkable differences in MS prevalence (generally, MS is significantly more frequent in northern than in southern parts of the world).
Fig. 2 The oligodendrogliopathy hypothesis. In the oligodendrogliopathy hypothesis, oligodendroglial apoptosis (by some undetermined causes) is the cause of demyelination and inflammation is a mere secondary event to clear up the degenerated myelin. See main text for the details.

1. The brain pathology, is, to a very great extent, a pathology of glia, which, when failing to function properly, determines the degree of neuronal death, the outcome and the scale of neurological deficit.

2. Glia acts as a brain warden, and as such it is intrinsically endowed with two opposite features: it protects the nervous tissue as long as it can, but it also can rapidly assume the guise of a natural killer, trying to eliminate and seal the damaged area, to save the whole at the expense of the part.