Is the transmembrane protein RCAS1 involved in evasion of the immune response in brain tumours?

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Introduction: It is well known that gliomas show very little if any immune response; however, the precise mechanisms are not fully understood. It is probable that in the case of gliomas there is active immunosuppression. The transmembrane protein RCAS1 has been suggested to play a role in suppression of the immune response to many malignant tumours outside the CNS, esp. carcinomas. RCAS1 protein acting through an as yet unidentified receptor can lead to apoptosis of immunocompetent cells, first of all so-called tumour infiltrating lymphocytes (TILs) – those belonging to the T-cell group [1]. RCAS1 has been shown to be expressed in many types of carcinomas such as endometrial and ovarian carcinomas. Very recently RCAS1 expression has been reported in gliomas [2].

Aim of the study: Investigations on the expression of RCAS1 in gliomas and brain metastatic carcinomas in relation to lymphocytic infiltration within tumour tissue.

Material and Methods: 41 brain tumours (10 metastatic carcinomas and 31 gliomas grade I-IV) were investigated for the expression of RCAS1 by immunohistochemistry. Labelling index (LI) of RCAS1 was calculated and compared with the intensity of lymphocytic infiltration.

Results: LI of RCAS1 in gliomas is related to the grade of tumour. In low-grade astrocytomas LI=5.12%, in high-grade gliomas LI=11.3%. In metastatic carcinomas LI RCAS1=15.1%. Of note, a strong expression of RCAS1 both in gliomas and in metastases was observed in many cells with morphological features of macrophages. The number of TILs/µm² was as follows: in low-grade gliomas 330.7, in high-grade gliomas 719.1, in carcinomas 1372.0.

Conclusions: In spite of similar level of expression of RCAS1 in carcinomas and malignant gliomas the number of TILs in carcinomas is significantly higher than in gliomas. RCAS1 expression was found to be significantly higher in high grade than low grade gliomas, which is in accordance with the report of Nakabayashi H. et al., who strongly suggested the role of RCAS1 in the evasion of immune response in gliomas [2]. The fact that carcinomas show a strong LI of RCAS1 and in spite of that they are intensely infiltrated by lymphocytes tends to lead to the conclusion that even if RCAS1 plays a role in the suppression of immune reaction to neoplasms in the brain this role is not crucial and there must be some other factors involved in this process. Moreover, according to our observations, it seems possible that it is the expression of RCAS1 in macrophages rather than in tumour cells themselves that is more important for the putative role of this protein in the suppression of immune response to the tumour.

References
Peripheral expression of microglial-related MIP-1α and IGF-1 in patients with Alzheimer’s disease. Important correlations with the clinical markers of disease progression

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It is well documented that the microglial-mediated inflammatory response contributes to the cell loss in neurodegenerative diseases presenting with dementia. Microglia may secrete toxic factors such as amyloid, proinflammatory products such as MIP-1α or reactive oxygen species and represent systemic concurrent processes or may represent a secondary response – a repair response to neuronal injury. The mechanisms underlying concomitant inflammatory reactions which contribute to neuronal degeneration and subsequent clinical signs are poorly understood. IGF-1 is involved in the regulation of cell proliferation and differentiation by acting as a neuroprotector and is expressed by microglia in the course of AD treatment. Since MIP-1α was established as a mediator of the inflammatory response and IGF-1 as a protector against neuronal death, they were target factors in our search for the influence on disease progression.

Peripheral levels of MIP-1α and IGF-1 were investigated in patients with dementia including AD and others and correlated with the clinical markers of disease progression represent by both the MMSE and the GDS tests. Extending the spectrum of clinical symptoms not assessed by the MMSE or the GDS tests, MIP-1α was correlated with some noncognitive signs such as behaviour, mood and personality changes.

Plasma samples for MIP-1α and IGF-1 analysis were stored at –80°C until processing. The levels of MIP-1α and IGF-1 were determined using enzyme-linked immunosorbent assay according to the manufacturer’s instruction (R&D Systems).

Among patients with AD, MIP-1α levels correlated positively with noncognitive impairment such as mood...
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Disturbances and personality changes. We found that MIP-1α did not correlate with the severity of dementia assessed by the MMSE as well as with the degree of disease progression assessed by the GDS test. Importantly, higher IGF-1 serum levels were responsible for the less advanced dementia.

Finally we conclude that a concomitant MIP-1α-mediated inflammatory response is responsible for the development of noncognitive signs and IGF-1 protects against the development of cognitive impairment in patients with AD.

[A4]

Intense hypertrophic astroglial reaction related to infiltration of primary malignant central nervous system lymphomas

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Primary central nervous system lymphomas (PCNSLs) arise in the CNS in the absence of lymphoma outside the nervous system at the time of diagnosis. The incidence of PCNSL has been increasing especially in AIDS patients, immunocompromised patients and immunocompetent elderly patients. The Epstein-Barr virus plays a major pathogenic role in immunocompromised patients with PCNSL. The majority of PCNSLs are classified as diffuse large B cell lymphomas. Other types of PCNSL are intravascular B-cell lymphoma, lymphomatoid granulomatosis, anaplastic large-cell lymphoma and post-transplant lymphoproliferative disorders. Microscopically PCNSLs demonstrate the typical angiocentric infiltration pattern. Sometimes PCNSLs show diffuse growth pattern with large areas of necrosis. In some cases of PCNSL astrocytic glial reaction may be prominent accompanied by hypertrophic forms of astroglial cells. These cases may be misdiagnosed as glial tumours.

[A5]

Microglia and astroglia in disturbances of cerebellar neuronal migration

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At every stage of central nervous system development neurones have a close association with, and functional dependence on, astroglial and microglial cells. A close relationship between neurons and glia exists in the proper development of the cerebellum. An investigation of morphological neuron-glia interactions in the abnormal cerebellar circuitry due to neuronal migration anomalies was the aim of the study. Two groups of neuronal migration disturbances were taken into consideration. The first (I) constituted abnormal groups of neurons arrested in the white matter of hemispheres during their way to the cortex. The second (II) represented disorganized cortical layering and gyrus formation.

I. The abnormal clusters of Purkinje and granular cells that lost their proper migratory way and settled in the white matter were surrounded by GFAP positive astrocytes, appropriate for surrounding white matter. There were no GFAP positive cells within the groups of heterotopic neurons. The intraheterotopic network of astroglia and neurons was organized differently from the normal cortical cerebellar network. The ramified microglial cells penetrated the parenchyma within the wrong located neurons, playing a role in their elimination.

II. The foci of disturbed gyros formation and disorganized cortical layering varied in size from small foci of marked disarrangement of cortical neurons to a blurred layered pattern of cerebellar cortex. In the cerebellar cortical malformations astrocytes were grouped near the Purkinje cells. In the minimal cortical malformations, such as fusion of external granular layers or nests of Purkinje neurons displaced to the internal granular layer, the increased number of astrocytes supported the neurons. The fused external cortical layers were underlined by GFAP immunopositive astrocytes located in the
molecular, Purkinje cells and external granule layers. The cells increased in number, size and GFAP staining intensity. The morphological features and distribution of microglia were similar to those observed in the age-matched controls. In the massive cortical malformation with the completely disorganized normal layered pattern of cerebellar cortex the degenerated astrocytes followed the disarranged Purkinje cells, while microglia was not present.

In the faulty formed cellular network the morphological interaction between glial cells and neurons was disturbed and this should have consequences on signal processing. The astrogial cells acted as regulators of neuronal activity, specially supporting the Purkinje neurons.

[A6]

Subset of reactive astrocytes in rat brain affected by perinatal asphyxiation

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Astrocytes are glia cells that play an essential role in the normal function of the nervous tissue and under pathological circumstances. Astrocytes become reactive in response to a variety of pathological stimuli and then they undergo hyperplasia, hypertrophy and enhance the production of glial fibres. Finally, astrocytes disappear as tissue lesions become purely fibrous scars. Accumulating evidence documents that reactive astrocytes also participate in neuroprotective mechanisms after brain injury. The specific marker of astrocytes is the glia fibrillary acidic protein (GFAP). However, the antibodies generated against this protein cannot differentiate between reactive and non-activated astrocytes. Since the results of recent studies suggest that neuroprotective effects of leptin and metallothioneines may be mediated by astrocytes, the aim of the present study was to localize reactive astrocytes in injured rat brains following neonatal asphyxia. In this experimental model only one brain hemisphere is injured; thus the contralateral hemisphere can be considered as an internal control. Nevertheless, a group of intact age-matched rats was included in our immunohistochemical study.

Our results show that two weeks after exposure to asphyxia, in the injured hemispheres large cysts were present, that were surrounded by GFAP immunopositive astrogliosis. In the contralateral unaffected hemisphere as in the brain of the intact rats, GFAP immunopositive astrocytes were present in the white matter and in the vicinity of some brain blood vessels. The metallothionein (MT) immunopositive cells were found only within the astrogliosis of the injured hemisphere. The same localization was observed for the cells that were immunopositive to leptin receptor (ObR) antibodies. The double stainings documented that MT and ObR immunopositive cells were GFAP immunoreactive astrocytes but no colocalization was observed when microglia detecting lectins or antibodies were used in the study.

In conclusion, our results show that the subset of reactive astrocytes can be differentiated from the other GFAP positive astrocytes by MT antibodies and that these cells express leptin receptors and may participate directly in the neuroprotective mechanism of leptin during brain healing.

[A7]

Confusing histopathological picture of advanced astrogliosis associated with haemangioblastomas

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Haemangioblastomas are often associated with cysts and an advanced gliotic reaction that sometimes mimics a neoplastic process of astrogial origin. The cyst wall is often formed by dense glial tissue composed of various astroglial elements such as reactive, gemistocytic and/or hypertrophic forms of astrocytes.
The reactive astrocytes participating in advanced glial response are often morphologically atypical and similar to neoplastic cells. The picture of small biopsies obtained from the solid gliotic wall of a cyst associated with a haemangioblastoma nodule might be confused with either pilocytic or diffuse astrocytoma.

We present some difficulties in differential diagnosis of a haemangioblastoma with predominant pilocytic or fibrillar pattern of surrounding gliosis. The compact gliotic walls of the cyst were composed of pilocytic astroglial cells with abundant Rosenthal fibres or compact gliosis with atypical features. In such cases the small tissue sample is not representative for primary tumour of haemangioblastoma origin and the incorrect diagnosis of either well-differentiated astrocytoma or diffuse infiltrating astrocytoma might be established.

In the human material, astrocyte reactivity was present but poor, and astroglial proliferation was seen only sporadically. Immunoreactivity of the astroglial cells to GFAP and S-100 was similar and rather mild, while to vimentin weak and present only in half of the examined cases. Only single astrocytes revealed the presence of tau protein. Similar astroglial reactivity was observed in the rat model of ALS except for the immunoreactivity to tau protein, which was seen in numerous astrocytes. Our study revealed that in ALS, astroglial reactivity was less intense than in other pathological processes. Weak immune reaction of astrocytes to GFAP and, especially, to vimentin indicates damage to astrocyte cytoskeleton and disturbed astroglial proliferation. Unknown aetiological factor(s) are responsible for ALS due to not only neuronal damage but also astroglial injury.

[A8]

Morphological changes in spinal cord astrocytes of transgenic rats in a model of familial amyotrophic lateral sclerosis – comparison with human amyotrophic lateral sclerosis


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We assessed astroglial reactivity within anterior horns of the spinal cord in patients with sporadic form of amyotrophic lateral sclerosis (ALS) and compared it with changes observed in transgenic rats in a model of familial ALS. The study was performed on 8 spinal cords of rats at the clinically silent period of the disease at the age of 60, 93 and 120 days, in 3 animals at the paretic stage and also in 10 human spinal cords of ALS patients who died at the age of 55-87 years. Formalin-fixed and paraffin-embedded tissue slides were stained by haematoxylin and eosin, according to Klüver-Barrera method and immunohistochemically with antibodies to S-100 protein, GFAP, vimentin, ubiquitin and tau protein.

In the human material, astrocyte reactivity was present but poor, and astroglial proliferation was seen only sporadically. Immunoreactivity of the astroglial cells to GFAP and S-100 was similar and rather mild, while to vimentin weak and present only in half of the examined cases. Only single astrocytes revealed the presence of tau protein. Similar astroglial reactivity was observed in the rat model of ALS except for the immunoreactivity to tau protein, which was seen in numerous astrocytes. Our study revealed that in ALS, astroglial reactivity was less intense than in other pathological processes. Weak immune reaction of astrocytes to GFAP and, especially, to vimentin indicates damage to astrocyte cytoskeleton and disturbed astroglial proliferation. Unknown aetiological factor(s) are responsible for ALS due to not only neuronal damage but also astroglial injury.

[A9]

Astroglial reactivity in a photochemical “ring” model of focal ischaemia in rats – brightness and shadows of the method


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For assessment of the astroglial reactivity in an animal model of focal ischaemia and the influence of MK-801 treatment, 10 normal adult rat brains and 10 rat brains after treatment were examined. Morphological changes were assessed on the 1st and 4th day after photochemical focal ischaemia triggered by ring irradiating beams with the diameters 0.35 mm and 0.55 mm. Formalin-fixed and paraffin-embedded tissue slides were stained by haematoxylin and eosin, according to Klüver-Barrera method and immunohistochemically with antibodies to S-100 protein, GFAP and vimentin.

On the 1st day after ischaemia, in the necrotic area, there was no immunoreactivity to GFAP and vimentin astrocytes, but some S-100 positive astroglial cells were present. In areas located more distantly from the necro-
sis, S-100 reactive astrocytes were more numerous and also a few astroglial cells immunolabelled by vimentin were found. Similar changes, although less pronounced, were observed in the cerebral hemisphere contralateral to the injury.

On the 4th day after ischaemia, in the necrotic area, astroglial reactivity was evident and more pronounced in the immune reaction to protein S-100 and vimentin than to GFAP. In areas distant from the necrotic focus, especially in the white matter, astroglial reactivity was more distinct than seen on the 1st day and more marked than in the contralateral hemisphere. There was no difference in astrocyte reactions in rat brains damaged by ring 0.35 and 0.55 mm as well as in normal rats and animals treated with MK-801.

Our study revealed that in the ischaemic focus destruction involved both neurons and astrocytes. In the injured hemisphere, in areas located more distantly from the necrosis, astroglial reactivity was evident and appeared earlier to vimentin and protein S-100 than to GFAP. In the hemisphere contralateral to the injury, astrocyte reactivity was also found.

[A10]

Neuropathological findings in adenylosuccinase deficiency

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Adenylosuccinase (ADSL) deficiency is a rare autosomal recessive disorder mainly affecting the nervous system. This devastating encephalopathy causes hypotonia, psychomotor delay and epilepsy. The disease may be diagnosed by detection of two abnormal metabolites in body fluids – succinyladenosine (S-Ado) and succinylaminomidazole carboxamide riboside (SAICAr). It is assumed that the former metabolite is neurotoxic. We report neuropathological findings in an infant affected with severe form of ADSL deficiency.

The girl was born in good condition, but from the beginning of life she was hypotonic, with poor suction. On her 7th day of life tonic-clonic seizures started with repeated episodes of apnoea and epileptic status. During the next period the baby was unconsciousness and progressively hypotonic. She remained on artificial ventilation till her death at 2.5 months. The EEG showed burst-suppression pattern. MRI of the brain at 1 month of age showed lack of myelination of cerebral hemispheres as well as enlargement of lateral ventricles. MRI at the age of two months showed cortico-subcortical atrophy and hypo- and dysmyelination of cerebral white matter mainly in occipitoparietal areas. The HPLC analysis of CSF fluid revealed elevated level of S-Ado and SAICAR, which confirmed the diagnosis of ADSL deficiency. Neuropathological data: Macroscopically the gyral pattern was normal, but there was failed operculisation of Sylvian fissures. Moderate atrophy of the brain with decrease of white matter volume, thinning of corpus callosum and enlargement of lateral ventricles were seen. White matter was mildly greyish, especially in posterior parts of the cerebral hemispheres. Cerebral cortex was not clearly delineated. Microscopic examination showed normal for age cytoarchitecture of the cerebral cortex. There was diffuse damage of the grey and white matter of whole central nervous system. The cerebral cortex showed severe damage and loss of neurons with several degrees of spongoid changes in the neuropil with scanty astrocytic glia reaction mainly of Alzheimer type II astrocytes. There was a correlation between the degree of loss of neurons and spongoid changes of the neuropile. The cerebral white matter also showed severe pathologic changes: the myelination was appropriate for the child’s age only in the posterior limb of the capsula interna, in the thalamus and mostly the paramedian part of the basal ganglia as well as in the brain stem and cerebellum. There was a complete lack of myelin in the centrum semiovale with spongoid changes, reduced number of oligodendrocytes, reaction of hypertrophic astrocytes and scanty macrophages in the most severe damaged white matter. The myelin and neuron fibres showed disintegration. In the myelinated part of the white matter there was seen a severe glia reaction positive in GFAP. There were signs of damage of astroglia with rarefaction and vacuolization of the cytoplasm and disintegration of glia processes. The oligodendrocytes were reduced.
in number except in structures of active myelination. The brain stem and cerebellum showed similar changes as in brain cortex and white matter. In the cerebellum the external granular layer was scanty, Purkinje cells showed severe loss and damage, the internal granular layer was severely damaged, and white matter in the axis of the cerebellum folia was very narrow with severe spongiotic changes. Many of the meningeal and brain vessels showed a thick wall, some brain vessels were surrounded by a large vacuole and disintegrated tissue with positive astroglial reaction. The topography of cortical and white matter damage was: the most severe changes were visible in the parieto-occipital and temporal lobes. The best preserved parts of the brain were the basal ganglia, thalamus and hypothalamus. Electron microscope evaluation showed enormous destruction of all cellular structures and myelin sheets; astonishingly the best preserved organelles were the mitochondria. The neuropathologic changes can be considered as the neurotoxic result of metabolic disturbances connected with adenylosuccinase deficiency.

The first method (method of cycloid) was based on cycloid function from Stereo Investigator Software (MicroBrightField). Length in 2D could be estimated from the number of intersections between a line-probe and the linear objects of interest. In our study we used a line-probe with systematically spaced sine-weighted curves (cycloids) of known length. In our study cycloids were 53.1 µm. The counting grid was constructed from sine-weighted lines (cycloids), which were used for estimation of length density of vessels.

The second method (skeletonization) was based on the use of mathematical functions of morphology and colour system transformation. The “binary airway tree” formed by the image segmentation step was skeletonized to identify the two or three-dimensional centrelines of individual branches and to determine the branchpoint locations. This idea was to utilize a skeletonization algorithm which exploits properties of the average outward flux of the gradient vector field of a Euclidean distance function from the boundary of the structure.

Method of cycloid. We observed a similar value of length density of vessels in the cortical grey matter between 11 and 16 GW (CGM – 0.06679 µm/µm). At 18 GW a decrease in mean length density of vessels was observed, in the cortical grey matter (CGM – 0.01189 µm/µm). A progressive increase was found in mean length density of vessels in cortical grey matter (CGM – 0.04255 µm/µm) and between 19 and 22 GW.

Skeletonization. We observed a similar value of length density of vessels both in the cortical grey matter between 11 and 17 GW (CGM – 0.032 µm/µm). At 18 GW a decrease in mean length density of vessels was observed, in the cortical grey matter (CGM – 0.01189 µm/µm). A progressive increase was found in mean length density of vessels in cortical grey matter (CGM – 0.04255 µm/µm) and between 19 and 22 GW.

Both of the methods (cycloid and skeletonization method) could be applied to measure length density of vessels in two-dimension (2D) sections. These morphometric methods enabled us to measure the length density in fetal development of vessels in cortical grey matter. The method of cycloid could be applied to measure an approximate length density to vessels. However, the skeletonization method could be applied to measure the precise length density of vessels in cortical grey matter.

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Correct vasculogenesis and angiogenesis in the fetal brain play a very important role in the appropriate proliferation, migration and maturation of neurones, glial cells and connection between structures.

In our study we examined 9 sections of fetal brains from gestation week (GW) 11 to 22. We measured length density (LD) of vessels (µm/µm) in cortical grey matter (CGM).

The aim of this work was to find a method which could be applied to measure the length density of vessels in two dimension (2D) sections.
[A12]

Oligodendrocytes within hypertrophic astrocytes (“emperipolesis”) in affected white matter in a case of MELAS

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Oligodendrocyte-astrocyte emperipolesis is an unclear phenomenon that was recently encountered in the white matter in some demyelinating and non-demyelinating diseases. We report for the first time the occurrence of oligodendrocytes within astrocytes in cerebral white matter in a case of mitochondrial syndrome of myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). Clinical history and postmortem neuropathological study of this female patient were presented at the Conference of Polish Neuropathological Association in 2006 (Wierzba-Bobrowicz et al.). In this study we present light and electron microscopic findings on brain biopsy, performed for diagnostic purposes 5 years after the onset of disease. Biopsy specimens from the parietal lobe disclosed laminar cortical cavitation accompanied by spongy rarefaction and enhanced cellular gliosis of subcortical white matter. Hypercellularity in white matter consisted of hypertrophic astrocytes, numerous small oligodendrocytes and scattered foamy macrophages. Occasionally small round nuclei of oligodendrocytes occupied the peripheral part of the cytoplasm of hypertrophic astrocytes. Ultrastructurally oligodendrocytes with well preserved nucleus and cytoplasm were seen within the cytoplasm of reactive astrocytes. The astrocytes engulfing oligodendrocytes displayed cytoplasm containing densely packed intermediate filaments, numerous small mitochondria and sometimes lipid droplets, pleomorphic bodies and axonal and myelin debris. It seems that in this case glial emperipolesis correlates with white matter damage associated with activated proliferation of hypertrophic astrocytes and non-myelinating oligodendrocytes.

[A13]

Glial cell abnormalities in frontal and temporal lobes of a chronic schizophrenic

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In schizophrenia a number of macroscopic and microscopic changes have been reported in the frontal and temporal lobes.

The study was carried out on 10 brains of chronic schizophrenics and brains of 7 patients (control group) who died without neurological disorders. Sections from frontal and temporal lobes were subjected to ultrastructural as well as histological and immunohistochemical examination by light microscope.

In the structures under study, a large number of neuroglial cells as well as microglial cells showing morphological abnormalities were noted.

Astroglia was usually in normal morphological condition around vessels and subpial regions. In the others areas of the cortex and white matter GFAP-immunoreactive astroglial cell bodies and processes were significantly reduced.

Most astroglial cells showed fragmentation of their processes. Sometimes reaction with GFAP was visible only around the nuclear membrane. The astrocytes had an oval/vesicular nucleus with marginated chromatin, and scanty cytoplasm.

At the ultrastructural level astrocytes were strongly damaged and revealed dystrophic alteration and signs of necrosis. Sometimes only the presence of gliofilaments was the only ultrastructural feature of astroglial cells.

Oligodendroglial cell density was reduced in the frontal and temporal cortex but these cells did not decrease in adjacent white matter. Oligodendroglial satellites of neurons were observed.

The electron microscopic observation revealed prominent dystrophic alterations and ultrastructural signs of apoptosis of oligodendroglia. Their cytoplasm was usually swollen with few cellular organelles. In oligodendroglia a number of cellular nuclei showed chromatin condensation.

Microglia showed on their surface the expression of the major histocompatibility complex class II (MHC II). Most microglial cells showed degenerative traits: cy-
toplasm shrinkage, thinning, shortening and fragmentation of their processes up to apoptotic changes. Perivascular microglia displayed the lowest intensity of degenerative changes. Ultrastructurally, some damaged microglial cells contained phagosomes and/or degenerated mitochondria.

Neuroglial (astroglia, oligodendroglia) and mesoglial (microglia) pathology in frontal and temporal lobes may reflect disturbances of neuron-glia interaction and may be related to neuronal dysfunction (survival, neurotransmission) and damage of their immunocompetent functions.