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Review Articles

Brain Mononuclear Phagocytic System and Degenerative Prion Diseases

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Several cellular units of the mononuclear phagocytic system could be found in brain: exogenous macrophages, perivascular cells, supraependymal cells and different type of microglia. With an important role in pathogenesis of the prion diseases (transmissible spongiform subacute encephalopathies) microglia are involved. It is still unknown whether pathological changes in these diseases, which include spongiform generation, nerve cell loss and gliosis, are the result of neurotoxicity of prion protein mediated by microglia or some other mechanism.

Key words: central nervous system (CNS), transmissible spongiform subacute encephalopaties (TSSE), prion protein (PrP), Creutzfeldt-Jacob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSSS).

Characteristics and type of degenerative diseases

The progressive dementia and neurological symptoms starting earlier or later in life are characteristic for the degenerative diseases of the nervous system. Huntigton's , Alzheimer's and Parkinson's diseases (non-prion degenerative diseases) share with transmissible spongiform subacute encephalopathies (prion degenerative diseases) common neuropathological feature-existing of abnormal insoluble proteins in CNS.

The main prion diseases include the several variants of the Creutzfeldt-Jacob disease and Kuru in humans, scrapie of sheep and goat and bovine spongiform encephalopathy of cattle ("mad cow" disease). The importance of the other rare prion diseases as fatal family insomnia, Gerstmann-Straussler-Scheinker syndrome in humans and transmissible mink encephalopathy, chronic wasting disease of mule, deer and elk is not so essential for the man's pahology.

Normally the rapid neurodegeneration in the prion diseases is preceded by a long period without clinical symptoms.

Brain mononuclear phagocytes and prion distribution within CNS

The prion hypotheses for the TSSE aetiology was put forth by P r u s i n e r [19] in 1982 and holds that the infectious agent consists of a conformationally changed normal cellular protein — PrPc. This protein is expressed by neurones and astrocytes and the last years there are studies indicating that activated microglia, a class of mononuclear phagocytic system in the brain, also express PrPc [3, 5]. Recent immunohistochemical data show in scrapie mouse brain specific distribution of the PrPc diffusely in neuropil, focally in amyloid plaques, in microglia and in 2-5 μm large structures resembling neuronal processes [4].

The pathologic (conformationally changed) prion protein —PrPsc or PrPres in addition to its association with infectivity seems to have neurotoxic properties which are mediated by microglia in the CNS [2, 14]. In vitro experiments suggest that neurotoxicity is dependent on the presence of microglia. That is indirect evidence for an early causative involvement of microglia in the development of spongiform changes [12, 23].

Microglia are glial cell type with controversial function but strongly characterized as brain mononuclear phagocytes with immune functions [10] . The degenerative prion pathology is always accompanied by astrogliosis — an increase in the number of nonneuronal astrocytes (a real astroglial hypertrophy) in contrast of the extensive microglial infiltration. Immunohistochemical investigation indicates only slightly increased markers for the macrophage or microglial activation [21]. The relative silence of the brain immunocompetent cells in situ (microglia, perivascular cells, exogenous macrophages) during clinical course of the prion diseases remains unsolved. Another typical change in the CNS of these disease is the nerve cell death [20, 13].

The role of mononuclear phagocytes to the propagation of the infectious agent

In total the contribution of the immune system cells to the propagation of TSSE is not well understood but perivascular microglia in CNS and follicular dendritic cells in the periphery may enhance the spreading and accumulation of pathologic prion protein (PrPres) [15] . Now there are data that the infectious agent for prion diseases is transferred from periphery into the brain by circulating cells of monocyte/macrophage lineage [9].

Specific humoral overproduction by microglia during the course of prion degenerative diseases

In vitro studies demonstrate that microglia elicit overproduction of pro-inflammatory cytokines IL1beta, and IL6 after exposure to the PrP 106-126 amino acids. In the same conditions the astrocytes over-express only glial fibrilary acidic protein(GFAP) [18].

The toxic effect of PrP in vitro to neurons is mediated by microglia via increasing their oxygen radical production [4].

Specific changes concerning brain mononuclear phagocytes during prion diseases

Recent data for the regional distribution and extent of the microglial activation during sporadic CJD show high levels in the grey (outer rim of spongy vacuoles) and white (diffuse response) matter. Double labelling with microglial markers and anti PrP demonstrate that microglia did not contain PrP immunoreactivity [17]. The immunohistochemical studies of a number cases of CJD make more clear the relationship between spongioform changes and microglial activation [22].

In experimental models (murine scrapie) are restricted to anatomical regions of the brain showing vacuolation, plaque formation and pathological accumulations of the prion protein [24]. Its very interesting that sometimes the pathologic PrP is detected within microglia during pathogenesis of scrapie infected mice [6]. An important fact is that during the clinical expression of murine scrapie the PrP deposition is detected after 30 days and microglial activation after 60 days [25].

In another prion disease as GSSS the presence of activated microglia in amyloid plaques was demonstrated by electron microscopy and immunohistochemistry (CD68, MAC387, Ricinus communis agglutinin-1 lectin) [1, 6].

Similar microglial association with plaque formation is described in Kuru [16, 11].

Phenotypic and functional changes in the resident mononuclear phagocytes of the CNS during the prion diseases are basic pathomorphological sign together with the prion deposition and neuronal loss. They could be estimated immunohistochemically and electronmicroscopically as an early specific indication of the clinical development of the transmissible spongioform subacute encephalopathies.

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