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Review Articles

Immunobiology of the mononuclear phagocytic system in central nervous system

D. Kadiysky, M. Svetoslavova

Institute of Experimental Morphology and Anthropology, Bulgarian Academy of Sciences, Sofia

The different central nervous system (CNS) pathology is accompanied by "gliosis" — an increase in the number of the nonneuronal cells — astroglia, microglia, exogenous macrophages. Some of these cell populations are representants of the mononuclear phagocytic system. They are perhaps the least well-characterized in the brain. The origin, the role and their relations with other cell types remains a controversial subject. The importance of the mononuclear phagocytic system in immunopathology and development is essential but its mechanisms are unexplained.

Key words: Mononuclear phagocytic system, CNS, microglia.

Introduction

The microenvironment of the central nervous system (CNS) has mechanisms of the selfprotection against injury, infection and immunologically unknown substances. The blood brain barrier makes this microenvironment partially privilege immunological region. Some of the elements of the mononuclear phagocytic system (MPS) — exogenous for the brain macrophages, perivascular cells, supraependymal cells, and different types of microglia can be easily found in the brain. Especially microglia is also one of the CNS glial cell types with controversial function, but strongly characterized as a class of MPS [13, 21, 22]. All these cells, commonly named "brain macrophages" are considered to play an active role in a variety of neurological diseases [12, 14]. Their functions in forming a network of immunocompetent cells within the CNS is supposable but not clear till now

Cell types of the mononuclear phagocytic system in the brain and its origin

Now the most important cellular forms of MPS can be defined as follows [4]:

ameboid microglia in white matter perinatally;

— ramified microglia in grey and white matter postnatally;

— activated microglia in areas of secondary reaction after nerve transection and CNS inflammation;

— reactive (phagocytic) microglia in areas of trauma, viral infection or neuronal degeneration;

— perivascular cells arround the small blood vessels and capillaries in the brain parenhyma with antigenpresenting and phagocytic functions (belonging to the resident microglia [4]);

— supraependymal cells.

The group of mononuclear phagocytic system in CNS is probably completed by ED2 — positive perivascular cells [11, 17], specialized phagocytic type with bone-marrow origin. In the same group we can include subependymal and epyplexus cells.

It's well known that the cells of the MPS in the brain are of multiple and different origin. The classical concept of del Rio Hortega (1932) [3] is in support of the cell unity of the MPS in CNS. This concept states that mesodermal elements invade the mammalian brain near the birthtime and remain scattered in the CNS throughout life, representing a source of microglia and macrophages in pathologic conditions [9]. Some authors suggest a blood-monocytic origin for ameboid microglia but the majority of resting microglial cells are of local, presumably neuroectodermal origin. Another conclusions [23] state that the normal adult CNS contains no cells belonging to the monocyte — macrophage lineage. But the majority opinions are that microglia belong to the mononuclear phagocytic system and originate from the blood monocytes-macrophages that invade the CNS in embrionic development [1, 4, 18]. Now there is agreement that microglia is a distinct class of MPS [7].

Characteristics and morphology of the MPS in the brain

Described under different terms the subpopulations of the MPS in CNS have a morphology very similar to other brain cells both in vivo and in vitro. Morphologically to make the difference is possible only between the ramified (resting, "quiescent") and the other cells of this system.

Microglia comprises between 5 and 20 % of the total glial cell in brain. Intercellular membrane contacts among microglia or between microglia and other neural cells have not been described in normal CNS [12]. Immunochemistry (monoclonal antibodies and lectins), enzyme histochemistry, metal impregnation and electron microscopy have been used to identify microglia. The resident microglia represents a major source of endogenous brain macrophages [8] and is thought to be involved in antigen presentation in vivo in CNS by virtue of the fact that they express major histocompatibility complex (MHC).

So-called "ameboid" microglia appears in the brain during the late stage of embriogenesis. These cells, with phagocytic properties disappear in postnatal period [2]. Morphologically they have been characterized by being round in shape and by exhibiting varying numbers of cytoplasmic vacuoles. They show high levels of lysosomal enzymes: acid phosphatase and non-specific esterase [5]. The "ramified" microglia appears pleomorphic, elongated or triangular with round or oval nucleus. The cells possess abundant, thin branches of cytoplasm, and contain a few primary lysosomes and varying numbers of secondary lysosomes.

In contrast to peritoneal macrophages microglia divides in culture [6]. Microglia exhibits functional characteristics common to cells of MPS: phagocytosis, Fc and CR receptors, MHC antigen expression, antigen presentation, interleukin-1 synthesis,

tumour cytotoxicity, superoxyde anion production and responsiveness to colony-stimulating factor [10]. The supraependymal cells have the phagocytic abilities of macrophages. The study of the other cell types of MPS in brain — subependymal and epyplexus cells is restricted by the absence of the procedures of their isolations.

It's clear that there are many difficulties in distinguishing all these populations — all of them possess a dendritic morphology and they are immunocompetent and phagocytic. They share features both of peritoneal macrophages and of the glial cells [6].

Cell markers and immunophenotype

For microglia the specific visualization with RCA-1 (*Ricinus communis* agglutinin 120) and GSA I-B4 (*Griffonia simplicifolia* B4 isolectin), widely used in histochemistry, are based on the presence of membrane associated glycoconjugates containing terminal α-D-galactose residues. A specific marker for ameboid microglia in vitro and ramified microglia in vivo, based on the phosphotyrosine immunoreactivity is proposed [26]. Another specific marker — OX-6 antigens, characteristic for the antigen-presenting cells in common is used for detection of activated microglia. The regional differences in the number of MHC class II antigen-presenting microglial cells in normal animals (OX-6 positive cells) correspond with the preferential sites of the eventual inflammatory infiltrates founded in EAE [27].

The OX-42 monoclonal antibody is specific for both ameboid and ramified microglia as well as for the cells of monocyte/macrophage lineage [20]. In the same time the OX-41 antibody labels only monocyte/macrophage lineage and not microglia [9]. This marker may be useful in discriminating microglia in CNS from blood-born phagocytes which invade the brain in pathologic lesions.

In tissue sections the ED1, ED2 and ED3 monoclonal antibodies label perivascular cells but not microglia. It is very interesting fact that relatively late in the course of EAE microglial cells in CNS are found to express ED1 antigen in their cytoplasm and this expression is probably a sign of phagocytic activity [10]. Common markers from this group for microglia and monocyte/macrophage cells are only ED7 and ED8. Minor differences in positive microglia markers are found between cultures derived from developing and mature central nervous tissue [10].

Discussion

As shown above it can be expected that the cells of MPS play a crucial role in the development and in the brain pathology. The experiments show a possible transformation of ameboid microglia into ramified during postnatal development. The term functional plasticity [24] refers to changes in microglial morphology, immunophenotype and functions that occur as the cells are confronted with a changing microenvironment, which will be result of pathology or normal development [25]. Microglia is implicated in wound healing, regulation of astrocytic differentiation, immune response and amyloid deposition in Alzheimer disease [20]. Whole specific cell pool of MPS in the brain plays an important role as immunological effector cells [19].

Activated microglia shows ameboidal shapes and has similar functions as monocytes-macrophages [21]. Ameboid microglia serves as principle scavenger cells during the development of CNS but during postnatal development it differentiate into ramified microglia, forming with the help of the other mononuclear phagocytes a potential immunoeffector network in adult brain [24].

Diseases where an active role for MPS has been proposed include AIDS [15], Alzheimer's disease and Multiple sclerosis [12].

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