ОГЛЯДИ

УДК 612.822:611.018: 616.8-003.98

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Microglia in normal condition and pathology

Мікроглія є одним із трьох типів гліальних клітин у центральній нервовій системі (ЦНС) і відіграє важливу роль як резидент імунокомпетентних і фагоцитних клітин у ЦНС при пошкодженнях і хворобах. Del Rio Hortego у 1927 р. відокремив мікроглію в окремий тип гліальних клітин, який відрізняється від олігодендроцитів і астроцитів. З 1970 р. минулого століття мікрогліальні клітини розглядаються як клітини, що виконують імунні функції в ЦНС і першими реагують на патологічні стани мозку. Мікроглія бере участь у ініціації та розвитку таких неврологічних патологій, як хвороба Альцгеймера, Паркінсона, розсіяний склероз, синдром набутого імунодефіциту за допомогою вивільнення цитотоксичних молекул, а саме: прозапальних цитокінів, протеїназ і комплементних білків. Існує багато доказів, які свідчать про те, що мікроглія може секретувати нейротрофічні фактори під час запалення або при пошкодженні мозку. У цьому огляді представлені сучасні дані про походження, морфологію та функціональні особливості мікрогліальних клітин.

Microglia, the major immunocompetent cells of the CNS [4, 16,] play a key role in brain pathology. During virtually any type of lesion, microglial cells are activated and transform in multistep process from a ramified morphology into an amoeboid macrophage – or dendritic cell-like (immune) phenotype [33, 49, 52,]. Microglial cells detect neuronal injury at a very early stage, and activation of microglial cells is limited to those anatomical regions occupied by the injured neurons. It is thus reasonable to hypothesize that neurons provide signals that regulate microglial activation.

HISTORICAL VIEW ON ORIGIN AND DEVELOPMENT OF MICROGLIA

The microglia as a distinct cell type was first recognized by Nissl who named them Staebchenyellen (rod cells) for their rod–shaped nuclei and considered them as reactive neuroglia [43]. It was del Rio Hortega, however, who advanced microglia as a distinct cell type apart from astrocytes and oligodendrocytes after his studies of brains from young animals using his silver carbonate staining method [12]. He believed that microglia originate from mononuclear cells of the circulating blood and have the ability to transform from resting ramified form into ameboid macrophages [11]. General view was that the microglia is derived from circulating monocytes or precursor cells in the monocyte–macrophages lineage that originates in bone marrow (Fig.1). These precursor cells invade the developing brain during the embryonic, fetal, or perinatal stages, and they transform from actively phagocytic globoid–ameboid form into resting ramified form of microglia in the normal mature CNS [3, 47]. There have been others who have proposed microglia of non–monocytes–macrophages lineage origin [31]. There are many opinions about the origin of the microglial cells: from circulating monocytes or progenitor cells form the line monocytes/macrophages; mesodermal origin; or neuroectodermal [2, 23, 29].

However, in recent times, the widespread opinion about the origin of microglia is Wolfgang Streit's ones, who considers that the microglia descends from the mielomonocytic row of hemangioblastic mesoderm and is the part of parenchyma of CNS in the early stage of embryonic development, when the process of neurolation already ended [50].

During of the embryonic and early postnatal period of the development microglial cells, besides phagocytic function, carry out also trophic function, produce the growth factors [54]; they participate in the maintenance of homeostasis [26], and they also contribute to axonal growth and vacuologenesis [50]. In the early postnatal period the amoeboid microglia concentrates in the zone of lateral ventricles. It is known, that in the developing brain there are 50–70% of neurons are dying from initial population, and therefore the assumption was made that the process of apoptosis can be signal for activation of microglia, which phagocytes decedent neuronal cells [14]. Furthermore, during this period of the brain development, the corpus callosum is formed, in which the nerve fibers connect two hemispheres. Therefore, by the following assumption, that explains of microglia arrangement in this zone, can be its participation in shaping of way for conducting the axons to the opposite side of the brain [2]. In the process of postnatal development in (1–15 days) the mi-

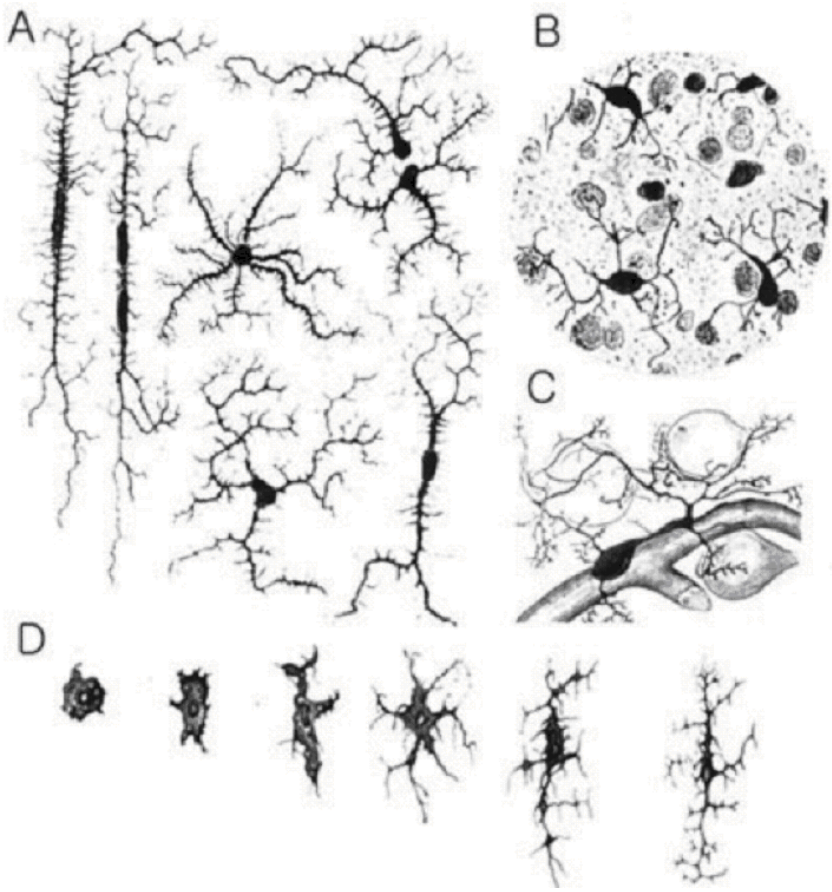

Fig.1. Microglia represented by earlier investigators. Brain sections were prepared after silver carbonate method of del Rio Hortega. A. del Rio Hortega (1932). B. Glees (1955). C. Penfield (1932). D. Kershman (1939) noted the amoeboid form of microglia originates from cerebral capillary wall, penetrates into various layers of the brain tissue, where the cell body begins to send out branches until the final resting state is reached. His study of the origin of microglia was undertaken in 22 human embryo brains of 8–27 weeks

croglia as the intermediate form with the thicken, short pseudopodia migrates from sub-ventricular zone throughout entire brain and to 15 days of postnatal development are differentiated [34].

GENERAL FEATURES OF MICROGLIAL CELLS

Microglia composes approximately 5% neuroglial cells in the white substance and 18% in the gray. Microglial cells have small size, the diameter of the cell body does not exceed 5–10 мм [33]. The numerous branches of different form are moved away from the body of each cell. Studies of the microglial cells ultrastructure in the norm showed that they have a nucleus of small size with the tightly complete perinuclear chromatin and the bright nucleoplasm. Electron-dense cytoplasm contains a small quantity of the organelles; for these cells noticeable characteristic is the rarely located granular endoplasmic reticulum, covered by ribosomes. Another evident feature of microglia is the presence of numerous filopodium and pseudopodium, also lysosomes and large quantity of vesiculae, which testify to the ability of microglia to the phagocytic activity [6, 30] (Fig.2).

At the early stages of postnatal period the microglial cells of amoeboid form are localized in the white substance of the sub-ventricular zone of the brain. Then microglial cells proliferate and migrate by the amoeboid motions and are converted into the intermediate subtype of microglia.

Intermediate microglial cells with the elongated branches and pseudopodia continue to

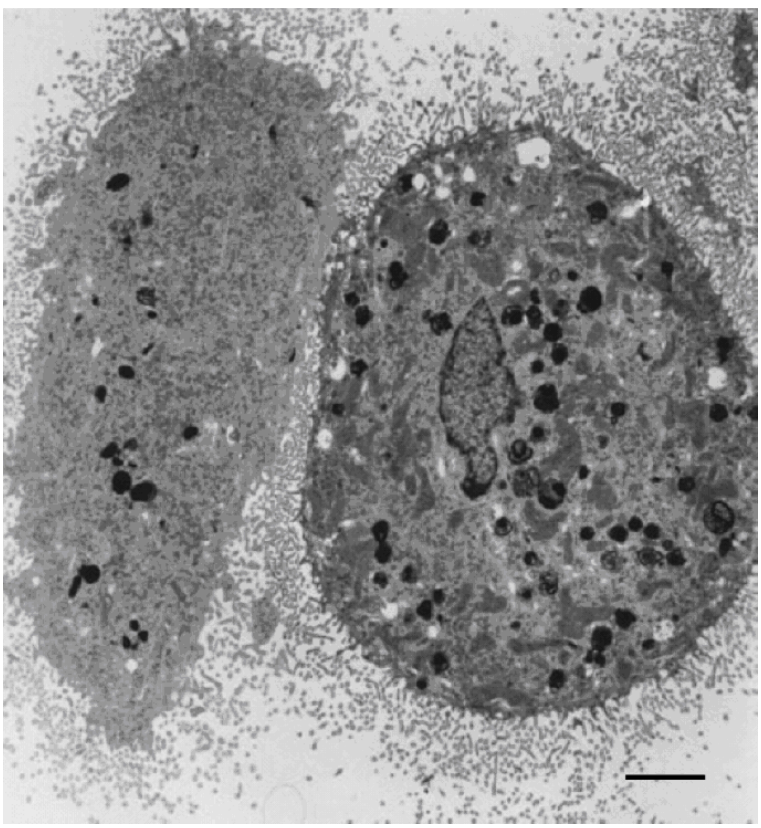

Fig.2. Electron micrograph of human microglia in culture. Note numerous filopodia and pseudopodia surrounding the cell surface, and well–developed dense bodies and vacuoles in the cytoplasm. Cultures were prepared from human brain from a 62–years old male. Scale bar 1 мм

proliferate and to extend throughout entire brain. These cells produce different growth factors, which are characteristic for this development period of the nervous system, such as the growth neurons factor (neutrofine–3), which is not produced in the adult brain.

Microglial cells separate on several subtypes by their functional properties. The microglia that is found in the state of rest (resting form), it is located evenly throughout entire brain and has the branched form. These cells take active part in the support of the brain homeostasis, by absorbing the toxic substances and the excess of the K^+ ions from the extracellular space [5, 13, 26].

Activated microglia is concentrated in the zone of interneuronal contacts during the damage of neurons and produce into the extracellular space large quantities different cytokines, such as interleukin-1 and the necrosis tumor factor, that in turn stimulate of astrocytic proliferation, causing reactive astrogliosis [34].

Depending on environment the activated microglia can acquire they bushy or rod-shaped form [48].

Phagocytic microglia is revealed in the areas of the brain damage by the virus infections and the areas of neuronal degeneration where microglia removes the debrises of neurons and other cells. Microglia/macrophage has rounded form with a small quantity of short branches [10, 32, 53].

MICROGLIA AS A FAGOCYTIC CELLS OF CNS

It would be correct to say that a major functional role of microglia in the normal CNS is that of sentry. This role, of course, is clearly analogous to the roles served by cells of immune system, such as macrophages and lymphocytes, in the rest of the body. The concept of microglia as the brain's immune system thus reconciles the discrepancy between the absence of leukocytes in the brain and the brain's ability to defend itself against infections, injury, and disease. With microglia, evolution has found a way to achieve compatibility between the destructive power of the immune system and the relative vulnerability of the CNS to injury and disease. Functionally speaking, one might therefore view microglia as a hybrid cell type that combines characteristics of a neural cell with some of the attributes of macrophages and lymphocytes [28]. Although the maintenance of microglia/brain macrophages in a cell culture was used and described in the 1930s, possibly even earlier, the procedure did not gain widespread popularity until the 1980s. The technique described by Giulian and Baker (1986) is now widely used with numerous modifications [17]. When culturing microglial cells, perhaps more so than with any other neural cell type, it is apparent that microglia in vitro are quit different from microglia in vivo. The preparation of primary mixed brain cultures, from which microglia are isolated, cause the generation of large amounts of tissue debris. This, together with a high serum content of the growth media, promotes rapid transformation of microglial cells into brain macrophages. Isolated microglia plated onto plastic culture dishes take on a rounded cell shape resembling that of immature amoeboid microglial precursor cells, and it was once widely accepted that cultured microglia are the same as amoeboid microglia. Since isolated microglia in vitro are essential brain macrophages, it is important to distinguish this advanced functional (phagocytic) state from the precursor state that defines amoeboid microglial cells in the developing CNS. Brain macrophages, like cultured microglia, secrete a variety of cytokines and growth factors, whereas amoeboid microglial progenitor cells do not [24].

Recently, cell culture techniques have provided new avenues of research in investigation of microglia. It is now possible to isolate microglia in mass from the brains of experimental animals and humans in the ab-

sence of any other contaminating cell types so that properties of microglia can be investigated in detail. Microglia cultures used most commonly were derived from newborn rat brain and produced very high cytotoxic molecules including proinflammatory cytokines, reactive oxygen intermediates, proteinases, and complement proteins [37, 38, 19]. Microglia–enriched populations could be prepared from primary cultures derived from human fetal telencephalon by collecting microglial cells that float freely in the medium in culture flasks. The purity of microglia in these cultures is more than 99% as determined by surface staining by *Ricinus communis* agglutinin 1 lectin (RCA) or CD11b [36, 40].

In vivo, microglia cells phagocytes cellular debris during the prenatal and early postnatal stages of brain development [46]. Axonal degeneration and neuronal cell death occur as a genetically programmed event during the CNS development to eliminate overproduced neurons and glial cells [45]. The dead and dying neurons and their degenerating processes provide the stimulus for the monocyte–macrophage lineage cell invasion of the CNS.

MICROGLIA PRODUCE CYTOKINES AND CHEMOKINES

It was considered to the recent times that the tissue of central nervous system is positioned out of the immune system inspection. The presence of blood-brain barrier, the absence of lymphatic system and the comparative ease, with that get adapted the sections of the brain under the transplantation, all this assumes the absence of immune response to the foreign antigens. As a result, CNS functions are not disrupted by massive allergic reactions, caused, for example, by the bite of bee. The proofs were obtained in favor of the fact that the microglia and the activated T-lymphocytes can enter into the brain and cause abrupt inflammation in cerebral tissue [41, 42]. The role of glia in interaction between the nervous and immune systems remains imperative and even more distant from the solution of problem.

Of critical importance in the prompt response of microglia to a variety infectious and inflammatory stimulus is their constitutive and inducible expression of large array of surface receptors that trigger or amplify innate immune responses. These include pattern recognition receptors implicated in the recognition of pathogen–associated molecules; complement receptors: cytokine receptors; and receptors that enhance macrophage effectors functions after interaction with the adaptive immune system, e.g. T cells or immunoglobulins (Fig.3). Because of the increased availability of immunological and molecular tools for examining receptors expression and for dissecting receptors–associated mechanisms, our understanding of the signals that may govern microglia immune functions in different pathological setting is just beginning to improve [1].

It is known that the microglia, as other cells of a mielomonotcytic row, produces cytokines and chemokines that participate in development and modulation of inflammation and regulation of homeostasis. It has been shown that the microglial cells of human under normal conditions (without the stimulation) express [mRNK] of IL-1в, IL-6, IL-8, IL-10, IL-12, IL-15, TNF-б [34].

By lipopolysacharides stimulation the expression of all cytokine/chemokine, with exception IL-15, considerably rises. Microglial cells also express mRNK of the receptors of cytokines IL-1RI, IL-1RII, IL-5R, IL-6R, IL-8R, IL-9R, IL-10R, IL-12R, IL-13R, IL-15R, TNFRI and TNFRII. Expression by the microglia of receptors for cytokines IL-1, IL-6, IL-8 and TNF-б indicates that they can react and be activated by these proinflammatory cytokines and further extend inflammatory reaction in CNS.

Important factor is the fact that the microglia of human expresses the receptors of

immunostimulating cytokines IL-5R, IL-12R, IL-15R, and also the receptors of proinflammatory cytokines IL-10R and IL-13R. These facts indicate that the activated microglia is the basic source of proinflammatory cytokines that cause inflammatory reaction in CNS, and the same time microglia possesses the ability to inhibit inflammation, producing IL-10R, through the autocrine– reversible correlation [30, 36].

There are a growth the research data, that evidence the fact of the hypersecretion of proinflammatory cytokines by the cells of CNS to promote of pathophysiological changes, that are observed under the different neurological diseases and the damages of the brain, and also that the basic source of these cytokine is the microglia. Therefore, activated microglia plays important role in initiation and development of the neurodegenerative diseases [19, 28, 35, 38].

IMMUNOHISTOCHEMICAL DETECTION OF MICROGLIA

The microglial plasma membrane is complex, containing variety of receptor and adhesion molecules in addition to enzymatic activities. Due to this large repertoire of surface antigens, numerous antibodies are now available to facilitate immunohictochemical staining of microglia, Interestingly, many of these monoclonal antibodies were not produced with the intention of specifically marking microglia, but were meant to target differentiation antigens found on cells of the immune system, such as macrophages, thymocytes, and lymphocytes. Following initial failure to demonstrate the presence of monocytic and lymphoid antigens on human microglia [44] it was found that a mouse macrophages–specific antigen could be localized on resting microglia with a monoclonal antibodies F4/80 [47]. These investigators also succeeded in showing the presence of Fc and complement receptors on resting mouse microglia using antibodies 2.4G2 and Mac–1, respectively. Analogously, ramified microglia in rat brain can be demonstrated reliably using OX–42 antibodies against CD11b antigen, also known as the CR3 *complement receptor* [20]. It is important to note that these receptors are also found on macrophages in neuronal tissues, and their presence on microglia underscores the phagocyt-

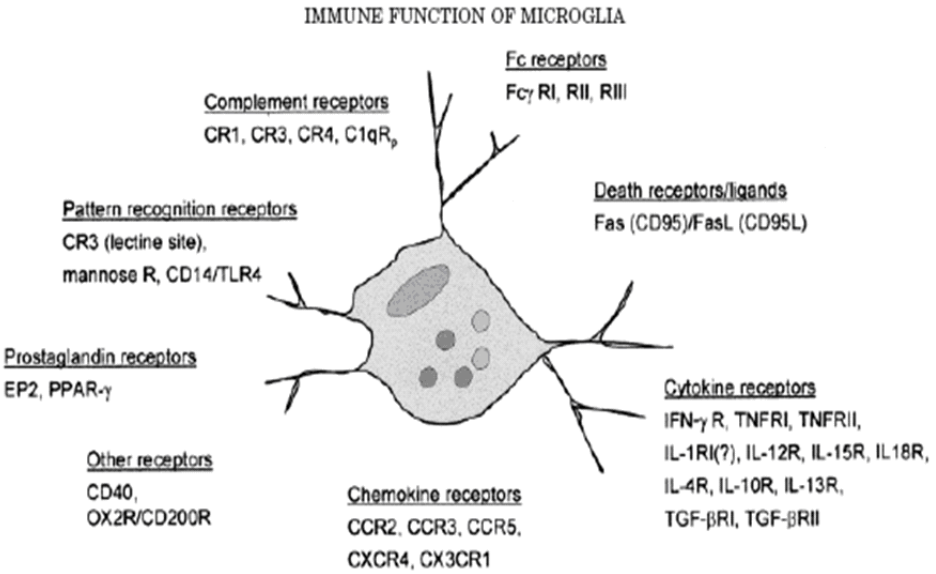

Fig.3. Signaling to microglia. Under inflammatory conditions, a variety of constitutively expressed and inducible receptors may promote migration as well as induce or downregulate immune effector functions of microglia

ic potential of these cells, as well as their close relationship to the myelomonocytic cell lineage. Cross–reactivity of macrophage–specific antibodies with microglia and blood monocytes has been taken as evidence that microglia are derived from monocytes. However, a direct lineage relationship between monocytes and microglia is not likely since both microglia and monocytes are fully differentiated cell types that may arise from a common precursor cell, as discussed above.

Immunohistochemical localization of ramified microglia has been achieved through the use of phosphotyrosine antibodies [21]. This procedure detects the products of an enzymatic reaction carried out by tyrosine kinase. There are important functional implications for this observation, since it is known that tyrosine kinase are often associated with cell surface receptors, which are plentiful on the microglial membrane. Various other immunohistochemical methods aimed at detecting somewhat unconventional antigen, such as vaults, ferritin, and lipocortin—1, have also been described [8, 27, 39]. Vaults, which is multiarched ribonucleoprotein particles of unknown function, appear to be enriched in microglia during ontogenety but mostly disappear in adult cells. Ferritin, on the other hand, is a well–known iron–store–age protein, and its detection in microglia suggests their active participation in iron metabolism, as in the case of blood monocytes and other tissue macrophages. Lipocortin–1 is Ca^{2+}– binding protein that is thought to function as an anti–inflammatory or immunosuppressive molecule.

In spite of a numerous quantity of antigens, such, as CR3 [15], MHC of the class of I and II [22], F4/80 [7], CD45 [9], phosphotyrosine [55] and others, that use for the identification of microglia, continues the search for the new markers, which would make it possible more adequately reveal entire population of microglial cells and to show the common picture of their distribution in the normal brain and in pathology.

In 1996 Imai Y., [25] for the first time insulated Iba-1 (ionized of calcium-binding of adapter of molecule 1) – ionized calcium–binding molecule, which specifically is expressed in the monocytic cellular line and in microglial cells. Iba-1 is begun to operate in the calcium signaling and is necessary for moving of cell and phagocytosis. Thus, Iba-1 can be used as new adequate marker for the development of microglial cells both within the normal and pathology.

SUMMARY AND PERSPECTIVE

Microglial cells have moved into the mainstream of neuroscience research, and their importance for maintaining issue homeostasis in the normal, and particularly in the injured, CNS is increasingly being, understood. The concept of microglia as the brain's immune system has become a widely accepted idea and, indeed, a very useful one because it emphasizes the unique structure of the brain in immulogical terms. The brain's immune system is essential for maintaining the organ's viability and functionality, and any impairment in its function could have detrimental consequences. Evidence is beginning to emerge that the brain's immune system is subject to aging–related deterioration and that microglial cell function may wane over the lifetime of an organism [51]. If dysfunction of microglia can be shown to occur with the advancing age, it could form the basis for a new perspective on aging–related neurodegenerative diseases such as Alzheimer's disease.

In sum, microglia have come a long way in a relatively short period of time: from barely being on the radar screen of neuroscience 20 years ago to taking center stage in theories regarding the pathogenesis of neurodegenerative disease today. With new knowledge on microglia accumulating rapidly, one can look forward to a day when treatment of microglia becomes the treatment of choice for brain dysfunction.

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MICROGLIA IN NORM AND PATHOLOGY

Microglia, one of three types of glial cells in the central nervous system (CNS), plays an important role as resident immunocompetent and phagocytic cells in CNS in the event of injury and disease. It was del Rio Hortego who in 1927 determined that microglia belong a distinct glial cell type apart from astrocytes and oligodendrocytes. Since 1970s there has been wide recognition that microglial cells are immune effectors in the CNS that respond to pathological conditions and participate in initiation and progression of neurological disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and acquired immune deficiency syndrome dementia complex by releasing potentially cytotoxic molecules such as proinflammatory cytokine, reactive oxygen intermediates, proteinases and complement proteins. There is also evidence to suggest that microglia is capable of secreting neurotrophic or neuron survival factors upon activation during inflammation or injury. It is thus timely to review the current status of knowledge on origin, morphology and functional features of microglial cells.

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Receved 17.03.2008