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Review

The microglia in healthy and diseased retina

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ABSTRACT

The microglia are the immune cells of the central nervous system and, also the retina. They fulfil several tasks of surveillance in the healthy retina. In case of an injury or disease, microglia become activated and tries to repair the damage. However, in a lot of cases it does not work, and microglia deteriorate the situation by releasing toxic and pro-inflammatory compounds. Moreover, they further promote degenerative processes by attacking and phagocytosing damaged neurones and photoreceptors that otherwise would possibly have the chance to survive. Such deleterious action of the microglia has been observed in degeneration of retinal ganglion cells and photoreceptors, and it takes place in hereditary diseases, infections as well as in case of traumatic or light injuries. Therefore, a number of attempts has been undertaken so far to inhibit the microglia, with varying success. The task remains to study behaviour of the microglia and their interaction with other retinal cell populations in more detail with respect to released factors and expressed receptors including the time points of the corresponding events. The goal has to be to find a better balance between helpful and detrimental actions of the microglia.

1. Introduction

It has been almost one century since the great Spanish physician and histologist Pío del Río-Hortega discovered the microglia as a novel cell population located in the central nervous system (CNS). He also discovered the oligodendrocyte and therefore added two new cell types to the previously known neurons and astrocytes.

For a long time, there was not known very much about these small cells with their long processes that were able to migrate and to phagocytose. However, with increasing opportunities of immunohistochemical techniques, cell culture and protein analysis, a lot of new insights were obtained about the behaviour and the role of the microglia in the CNS, and it is difficult to overview all the information that is available about microglial cells so far. In this review, we focus on the microglia in the retina, its role in diseases and some microglia-directed therapeutical approaches.

2. General historical aspects of microglia and its origin

Río-Hortega was the first who declared the microglia as a population in the CNS that are distinct from neurons and astrocytes and called them bodyguards, “which spread their tentacles everywhere and deter anything which could cause harm” (del Río-Hortega, 1933). Marchesani was the first who labelled them in the optic nerve and inner layers of the retina in eyes from rabbit, monkey, cat and man using Hortega's staining technique (Marchesani, 1926). In this special histological protocol, tissue samples are fixed in formalin, frozen sections are made and immersed into silver nitrate and sodium carbonate with ammonia hydroxide for 10 min. After washing, the samples are treated with gold chloride, washed again and mounted on glass slides (Marchesani, 1926). Marchesani also discussed some early findings that were known about microglial cells at that time, *e.g.* their late appearance in the nervous tissue during embryonic development and their ability to actively migrate through the nervous tissue and to phagocytose, in the author's opinion most probably normal and pathological metabolites. Hortega's stain was applied to detect microglial cells for a long time, *e.g.* in 1970 by Vrabec (1970) who labelled the microglia in the outer plexiform layer of the retina of monkeys and rabbits, or by Ling (1982a), who demonstrated microglial cells in the retina of rats.

2.1. Origin from mesodermal cells

The origin of the microglia had been disputed for a long time. Río-Hortega hypothesised that the microglia could be derived of the pial mesenchyme, and therefore sometimes used the term “mesoglia” (del Río-Hortega, 1933). The view of a mesodermal origin of microglia was widely supported by a lot of other authors

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including Cammermeyer (1970), Boya et al. (1979), Ashwell (1991), Kettenmann et al. (2011), Marin-Teva et al. (2011) and Eyo and Wu (2013). Boya et al. (1979) reported that microglial cells came from acid phosphatase positive cells in the meninges of newborn rats. Later on, they used isolectin and *Ricinus communis* agglutinin histochemistry to reinforce that the microglial cells were derived from the infiltration of meningeal connective tissue cells (Boya et al., 1991). Dalmau et al. (1997) demonstrated that microglial precursors may originate from different mesodermal sources on different embryonic age and then transform into microglial cells.

2.2. Origin from developing nervous system

Other authors connected microglial ontogeny to the developing nervous system. Hutchins et al. (1990) suggested that the microglia were originated in the germinal matrix. Kitamura et al. (1984) claimed that the microglia developed from glioblasts and were of neuro-ectodermal origin. Hao et al. came to the same conclusion after culturing embryonic astroglial cells under nutritional deprivation or exposure to colony stimulating factor 1 (CSF-1), which resulted in a production of macrophage-like cells (Hao et al., 1991; Richardson et al., 1993). Alliot et al. (1991) also deduced from their *in vitro* experiments that microglial cells are derived from the parenchyma of various part of the brain. De Groot et al. (1992) distinguished between “brain macrophages” and “resting microglia” and postulated that brain macrophages had their origin in the bone marrow, whereas the “resting” microglial cells were of neuroectodermal origin. Although the authors stated that they did not find transitions between brain macrophages and “resting” microglia, it appears to be likely that the invading microglia first had a macrophage appearance and then turned into the “resting” microglia rather quickly. Some studies strongly advocated that microglial cells are neuroepithelium-derived because the monoclonal antibody lipocortin-1, which labelled the microglial cells, can also label the neuroepithelial cells (Fedoroff et al., 1997; McKanna, 1993a,b).

2.3. Origin from monocytes/macrophages

Monocytes have been reported in a lot of studies as one source of microglial cells. Ling et al. (1980) used colloidal carbon particles as an intracellular marker to confirm that monocytes can enter into the developing rat brain and transform into microglial cells. In 1985, Perry et al. (1985) first used the macrophage specific antigen F4/80 to label microglial cells in immunohistochemical study, and reported that microglial cells had originated from monocytes as macrophages. Using cortisone and dexamethasone to suppress the production of blood monocytes, a significant reduction of microglial cells can be found in the corpus callosum (Ling, 1982b; Kaur et al., 1994). Htain et al. (1994) reported that the number of microglial cells was significantly reduced in the brain of athymic nude mice than the normal mice. They attributed this result to the lack of thymosin, which is produced by the thymus gland and is essential for the maturation of monocytes. The above-mentioned authors suggested that microglial cells derived from monocytes. Hickey and Kimura (1988) showed that perivascular microglial cells were derived from bone marrow. Eglitis and Mezey (1997) transplanted adult mice with donor bone marrow cells and demonstrated ability of cells derived from the transplant to enter the CNS and give rise to astrocytes and microglial cells. The authors concluded that at least part of microglial cells were of bone marrow origin. There are more reports that in the neonate and adult organism, microglial cells may derive from circulating blood monocytes originating primarily from the bone marrow, traverse along the blood vessels and finally populate in the nervous system (Perry et al., 1985; Rezaie and Male, 2002).

Haematopoietic progenitor cells were regarded as one possible source of microglial cells in a lot of studies (Asheuer et al., 2004; Hess et al., 2004; Vallières and Sawchenko, 2003; Vitry et al., 2003). However, Ginhoux et al. (2010) challenged the postnatal haematopoietic progenitors as the origin of microglia. Through reconstituting irradiated C57BL6 CD45.2^{+} newborn mice with haematopoietic cells isolated from CD45.1^{+} congenic mine, they found that almost all of the adult microglia remained host original after transplantation. With performing different lineage tracing studies, they concluded that postnatal haematopoietic progenitors, including monocytes, do not significantly contribute to microglia homoeostasis in the adult brain, and adult microglia most probably derive from primitive macrophages.

2.4. Origin from the yolk sac

A novel point of view was brought into the discussion in 1999 by Alliot et al. based on findings that some haematopoietic cells are generated in the yolk sac. The authors showed that some microglial progenitors can be detected in the early neural folds at the 8th embryonic day, and that the number of cells rapidly increases to reach a plateau during late gestation. Therefore, they concluded that microglial progenitors derive from yolk sac, colonise the brain rudiment during early developmental stages and reach their final number by an active proliferation in the brain (Alliot et al., 1999). Later on, Chan et al. (2007) reviewed the concepts of microglial origin and stated that “they could derive from progenitors located in the yolk sac”, however, still discussed other possibilities.

Ginhoux et al. (2010), Schulz et al. (2012) and Mizutani et al. (2012) also supported the claim that the microglia derive from the yolk sac and are genetically distinct from haematopoietic stem cell progeny. Schulz et al. (2012) reported that although the transcription factor Myb was required for the development of haematopoietic stem cells and all CD11b^{high} monocytes and macrophages, the differentiation of F4/80^{bright} macrophages was not affected by Myb deficiency. These macrophages include liver Kupffer cells, epidermal Langerhans cells, and microglial cells (Schulz et al., 2012). Golub and Cumano (2013) drew the similar conclusion that the yolk sac produces myeloid cells that migrate to the central nervous system to form the microglia and to the skin to form the Langerhans cells. Kierdorf et al. (2013) found that mouse microglial cells were derived from primitive CD45^{-} c-kit^{+} erythro-myeloid precursors (EMPs) which were first detected in the yolk sac at embryonic day (E) 8 and developed into CD45^{+} c-kit^{-} microglia. They also found that Myb was not required for the development of microglia. Perdiguero et al. (2014) confirmed these findings. They demonstrated that in mice the vast majority of adult tissue-resident macrophages including microglial cells in the brain originated from a *Tie2*$^{+}$ cellular pathway generating *Csf1r*$^{+}$ EMPs, which are distinct from haematopoietic stem cells (HSCs). EMPs firstly develop in the yolk sac at embryonic day E8.5, then migrate and colonise in the foetal liver. Until E16.5, EMPs give rise to foetal erythrocytes, macrophages, granulocytes, and monocytes. However, most of these cells will be replaced by HSC-derived cells except some kinds of macrophages. Microglial cells, Kupffer cells and Langerhans cells are only minimally replaced by HSC-derived cells. The authors concluded that yolk sac EMPs are a common origin for adult tissue macrophages including microglial cells (Perdiguero et al. 2014). Ginhoux et al. (2013) and Katsumoto et al. (2014) reviewed recent findings of microglial origin from the yolk sac and the role of the microglia and monocytes in neurodegenerative diseases.