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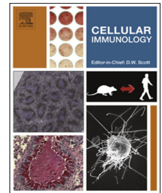

Research paper

New concepts in macrophage ontogeny in the adult neural retina☆

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ABSTRACT

The number of neurons dedicated to vision itself is thought to be greater than the sum of the four other senses combined. Yet, little attention has been payed to the retina as compared to elsewhere in the central nervous system with respect to microglia, the macrophages of the neural parenchyma. Indeed, major advancements in the understanding of microglial ontogeny and maintenance in brain and spinal cord are now widely appreciated, whereas less notice has been given to the neural retina in this regard. The current Review covers topical concepts on adult microglia and perivascular macrophage ontogenies in the steady state retina, as well as parallels made with these macrophages in other areas of the central nervous system. The subject of recruited monocytes and their descendant monocyte-derived macrophages in degenerative diseases of the retina is also integrated into this Review. Key experiments that have led to the theories covered are highlighted throughout, as are the knowledge gaps that remain unresolved.

1. Scope of this review

The last ten years have seen major leaps in our understanding of macrophage development, including microglia in the central nervous system (CNS). Perhaps the foremost important of these advances is the discovery of the embryonic origin of adult microglia [1], which has changed the way many in the field think about these cells in health and disease, including in the visual system [2]. This new knowledge has led to a better handle of macrophage (MF) ontogenies in the periphery as well [3–11], as reviewed elsewhere [12]. In addition, novel findings regarding the ontogeny of perivascular MFs in the CNS are also of major interest [13] and reviewed here.

Inroads to our understanding of MF networks have likewise been made in another key region of the CNS – the neural retina. The purpose of this Review is to provide new information regarding MFs in the neural retina, with a central focus on ontogeny of microglia and perivascular ones. Also reviewed here are recruited monocytes (MOs) and MO-derived MFs (MO-MFs) in animal models of retinal degenerative diseases, such as in retinitis pigmentosa, and with relevant points in age-related macular degeneration (albeit with a focus on the neural retina). The optic nerve (which is also part of the CNS) and the choroid (which is not part of the CNS) are likewise crucial components of the visual system (Fig. 1). However, less is known about the ontogeny of their MF networks, and this Review does not focus on these tissue compartment [14].

2. Ontogeny of retinal microglia in homeostasis

Microglia primarily reside in the synaptic regions of the retina, called the inner and outer plexiform layers (Fig. 1). Recent data suggest that their origins in adult mice may arise from the embryo, like the brain. Indeed, these cells have been shown to be long-lived, which is reviewed below; and, there are data suggesting microglia are self-renewing [15–17]. Also similar to elsewhere in the CNS, microglia are *not* bone marrow (BM) derived including the retina. Together, these data point toward an embryonic origin of adult retinal microglia; however, direct evidence that they are indeed embryonic-derived is still lacking. Such unresolved knowledge gaps, as well as the key experiments and concepts that have led to the current understanding of retinal microglia ontogeny are reviewed in this section.

2.1. Irradiation-bone marrow transplantation: (Mis)-lessons in physiology

Similar to elsewhere in the CNS, generation of BM chimeras via whole body irradiation of wildtype hosts and subsequent transplantation of GFP^{+} donor BM was a generally used system to study microglia in the retina. As such, experiments pioneering the use of this system to study the retina had examined questions involving steady state turnover of microglia, or recruitment of circulating myelomonocytic cells following injury or induction of a diseased state [17–21]. However, it is now understood that this irradiation-transplantation regimen results in

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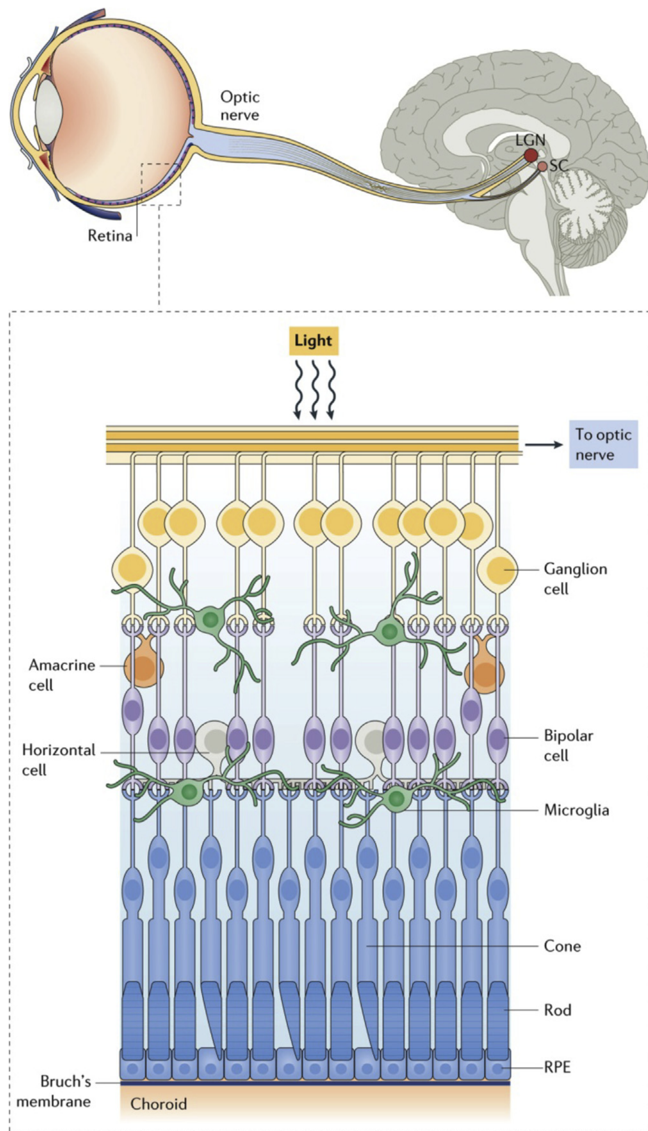

Fig. 1. Anatomy of the retina. The neural retina extends from the bottom of the photoreceptors (i.e. outer segments of rods and cones) to the retinal ganglion cell axons of the nerve fiber layer in the superficial retina. *Originated from* [2].

nonphysiological engraftment of donor BM derived MFs, of which eventually out-populate host endogenous microglia. This phenomenon is in contrast to physiological conditions, as we now appreciate that endogenous microglia are maintained *in situ* throughout life and MO recruitment is restricted from entering the CNS in the steady state.

Two seminal papers helped make the discovery that MF engraftment in brain and spinal cord as seen in irradiated-transplanted hosts is *not* physiologic [22,23]. The landmark paper by Ajami et al. combined irradiation and parabiosis techniques to address this question in spinal cord and brain stem. They showed that myeloid cells provided through a GFP$^+$ parabiont was not sufficient for engraftment to occur in the CNS of an irradiated wildtype partner, whereas irradiation and BM transplantation was sufficient [22]. Taking another approach, Mildner et al. applied lead head shielding to mice during irradiation, prior to BM transplantation. They found that shielding protected brain from engraftment, whereas engraftment was readily detectable in the unshielded spinal cord of the same mouse [23]. Together these papers demonstrated that irradiation and BM transplantation are both necessary to condition the CNS for engraftment of BM-derived MFs.

In addition, Mildner et al. showed that engraftment involves Ccr2, the Ccl2 chemokine receptor involved in egress of MOs from BM into the circulation. This finding suggests that engrafted cells involve MO-derived cells [23]. Interestingly, however, the follow up paper by Ajami et al. pointed to uncommitted progenitor cells (as opposed to myelomonocytic-committed hematopoietic cells) as the contributors of engrafted MFs in irradiated-transplanted hosts [24]. Elegant work by Bruttger et al. supports this hypothesis as well [25]. Hence, although it is established that donor BM indeed contributes to engrafted MFs in this setting, there are still open questions pertaining to the precise precursor cells in the BM that dominantly give rise to this engraftment.

For the neural retina, original irradiation-transplantation work also showed the appearance of donor BM-derived MFs in this setting [17,20]. However, at the time it was still not known that this phenomenon is nonphysiological, as opposed to potentially normal turnover of retinal microglia. O'Koren et al. addressed this knowledge gap by setting up GFP$^+$ BM chimeras in mice that were either protected with lead head shielding or not-during irradiation [26]. Authors demonstrated that the neural retina of head shielded mice did *not* undergo engraftment of donor BM-derived MFs, whereas engraftment was readily detected in unshielded mice [26]. The latter finding corroborated previous work by Chen et al., who showed that engraftment of donor BM-derived MFs in the neural retina involved Ccl2-Ccr2 signaling [20]. In summary, engraftment in the neural retina of irradiated-transplanted hosts represents a nonphysiological setting, and thus the BM does not contribute to the normal pool of microglial in the neural retina.

2.2. Microglia ontogeny

If adult hematopoiesis does not contribute to the pool of microglia under normal physiologic conditions, then where do they originate? In a seminal finding by Ginhoux et al., adult microglia were shown to arise directly from the embryo [1], by cells called erythromyeloid progenitors (EMP) [11,27,28]. This finding has changed the field [29], a topic touched on later in this Review with respect to the retina. Authors made this finding by transferring a technique more commonly used by developmental biologists in cell lineage tracing. Specifically, they tamoxifen pulse-labeled embryos in pregnant *Runx1*$^{MER\text{-}CRE\text{-}MER}$; *R26*^{YFP} dams and were able to show that brain microglia in the adult progeny were YFP$^+$ [1]. Hence, not only did this experiment 'trace' adult microglia back to the embryo (specifically to the yolk sac), but these data also demonstrated indirectly that microglia are long-lived. Together with other work, the current understanding is that brain and spinal cord microglia are embryonic-derived, long-lived and self-renewing, like many other MFs in the periphery [3–11,13,22,24,25,27,28].

For the retina, O'Koren et al. established that microglia are long-lived in the adult neural retina [26]. In this paper, GFP$^+$ donors were used to generate lead head shielded BM chimeras, which showed that microglia were unanimously GFP$^-$ at six months post transplantation and at later time-points. Contrastingly, in chimeras that underwent whole body irradiation (no shield), retinal microglia were eventually out populated by BM-derived MFs (GFP$^+$) [26]. Also, O'Koren et al. took advantage of tamoxifen pulse-labeled *Cx3cr1*^{CreER} mice [30,31]. Specifically, *Cx3cr1*$^{eYFP\text{-}CreER}$; *R26*^{tdT} mice were pulse-labeled (Fig. 2), showing that retinal microglia retained their tdT$^+$ label for six months post tamoxifen administration, and at later time-points [26]. This finding corroborated the long-lived status of retinal microglia shown in the lead shielded chimeras. O'Koren et al. was later recapitulated by Ma et al. in the neural retina, and likewise by Goldmann et al. using the same strategy to study longevity of brain microglia [32]. Hence, the long-lived status of retinal microglia is now established, and there is evidence to indicate self-renewing as well [15–17]. Nonetheless, whether retinal microglia are embryonic derived (like their counterparts elsewhere in the CNS) has still not been investigated.

To summarize, irradiation-transplantation is a nonphysiological setting and thereby engraftment of BM-derived MFs is *not* the process

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