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Retinal ganglion cell death in glaucoma: Exploring the role of neuroinflammation

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ABSTRACT

In clinical glaucoma, as well as in experimental models, the loss of retinal ganglion cells occurs by apoptosis. This final event is preceded by inflammatory responses involving the activation of innate and adaptive immunity, with retinal and optic nerve resident glial cells acting as major players. Here we review the current literature on the role of neuroinflammation in neurodegeneration, focusing on the inflammatory molecular mechanisms involved in the pathogenesis and progression of the optic neuropathy.

1. Introduction

The concept of the central nervous system (CNS), including retina and optic nerve, as "immuno-privileged" and with limited communication with the immune system due to the presence of the blood brain barrier (BBB) has quite evolved in the last ten years. Although the peripheral access of the immune response to the CNS is restricted and tightly regulated, it is now clear that the CNS itself is immune competent and it is able to orchestrate a coordinated immune and inflammatory reaction in response to a variety of insults (Rivest, 2009). Furthermore, circulating immune cells from the periphery can readily enter into the CNS under pathological states and conditions that alter the BBB and the blood-ocular-barrier.

Neuroinflammation has recently gained attention as one of the common hallmarks in both acute and chronic neurodegeneration (Amor et al., 2014). Indeed, neuroinflammation has been identified as an important component of primary and secondary neurodegenerative diseases, like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), stroke and epilepsy (Frank-Cannon et al., 2009).

Glaucoma is recognized as a neurodegenerative condition characterized by the progressive loss of retinal ganglion cells (RGCs) associated with typical visual field defects and specific alterations of the optic nerve (Quigley, 2011). Elevated intraocular pressure (IOP) is considered, along with advanced age, the main risk factor for the optic neuropathy (Leske et al., 2007). Drugs targeting IOP are currently the only FDA-approved to treat the disease (Bucolo et al., 2013). However, the relatively high incidence of normal tension glaucoma and the absence of glaucoma signs in people with elevated IOP, as well as the often observed progression of neurodegeneration in patients with pharmacologically controlled IOP, makes it clear that the triggers, leading to the damage and the following degeneration of RGCs, are still not defined. Alteration of neurotrophin signaling, oxidative stress, excitotoxicity, mitochondrial dysfunction, protein misfolding, hypoxic and ischemic phenomena have all been indicated as potential contributors (Qu et al., 2010). Along with these putative factors, inflammatory mechanisms may also play an important role in the degeneration of RGCs, since inflammatory responses have been identified as common features in glaucoma, either

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clinical and experimental (Karlstetter et al., 2015; Ramirez et al., 2015; Soto and Howell, 2014; Tezel, 2013; Tezel and Wax, 2004b; Vecino et al., 2015). Therefore, the view of the immune system in the pathophysiology of glaucoma is gradually evolving and evidence have been now provided for either neuroprotective and detrimental functions of the inflammatory process in RGC degeneration.

2. The players of neuroinflammation

The term "neuroinflammation" refers to the reaction of immune-competent cells and other cell types (i.e. neurons and astrocytes), which occurs in the CNS in response to several insults spanning from infections to trauma, ischemic events, deposition of altered proteins etc. The aim of neuroinflammatory response – which involves the proliferation of microglia and astrocytes, and the release of a plethora of pro- and anti-inflammatory cytokines, neurotransmitters, chemokines and reactive oxygen/nitrogen species- is, overall, to counteract the insults and buffer their damaging effects. However, the final outcome will depend mainly on the severity and the duration of the neuroinflammatory process (Vivekanantham et al., 2015).

In the brain microglia and astrocytes are the tissue resident immune-competent cells that initiate the inflammatory response. Microglia are resident macrophages derived from myeloid progenitors, which are thought to be the main cell type of the innate immune system in the brain acting as first responders against pathophysiological stimuli. Astrocytes are cells of neuroectodermal origin able to respond to pathological stimuli through reactive gliosis and the release of pro-inflammatory cytokines. Resident immune cells constantly survey the brain for pathogens and support CNS homeostasis and plasticity by playing critical functions in axonal growth, synaptic remodeling and neuronal survival (Dheen et al., 2007; Prinz and Priller, 2014).

Following a detrimental insult or infection, microglia senses alteration in the tissue by the identification of so-called damage or pathogen-associated molecular patterns (DAMPs and PAMPs) and becomes "reactive" or "primed" (Prokop et al., 2013). Resting microglial cells show small somas and ramified aspect, while once activated they are characterized by an amoeboid shape with short and stout processes and become phagocytic and mobile (Beynon and Walker, 2012).

Among the receptors expressed by microglia and astrocytes that mediate the pattern recognition, toll-like receptors (TLR) play an important role (van Noort and Bsibsi, 2009). Following TLR-mediated activation, microglia and astrocytes release several soluble factors, including chemokines and cytokines, which can either exacerbate neuronal damage or promote neuronal survival.

Some of the factors, released from the "so-called" reactive microglia, lead to the activation of astrocytes that amplify the immune-signal, and induce alterations in the BBB, allowing the recruitment and infiltration of monocytes and lymphocytes (Hickey, 1999; Taupin et al., 1998). The further release of inflammatory mediators may lead to a self-sustaining, uncontrolled, loop that results in secondary neuronal damage (Das and Basu, 2008; Whitney et al., 2009).

Mounting evidence suggests that activated microglia, similar to macrophages, has two alternative phenotypes, distinguishable by a different gene expression pattern: M1 and M2. Each phenotype secretes a different array of cytokines (Pisanu et al., 2014). While M1 phenotype contributes to the amplification of the pro-inflammatory response during injury and infection by releasing pro-inflammatory cytokines (i.e. TNF-α, IL-1β, IL-6 and IL-12) and cytotoxic mediators like superoxide, nitric oxide and reactive oxygen species, M2 microglia produces a variety of anti-inflammatory cytokines (i.e il-4,(i.e. IL-4, IL-13, IL-10 and TGF-α) antagonizing M1 response, promoting the tissue repair and acting as immunosuppressors (Pepe et al., 2014; Tang et al., 2014).

It has been suggested that during the early response to an injury, the majority of the microglia expresses an M2 associated array of genes, while M1 gradually becomes predominant in later stages (Hu et al., 2012; Wang et al., 2013a, 2013b). Therefore, microglia activation, polarized toward the M2 phenotype, may be beneficial in the early stage of neurodegeneration (Cagnin et al., 2006; Hu et al., 2012; Tang et al., 2014), while, long-term overactivation, associated with the upregulation of pro-inflammatory cytokines, might contribute to the neurodegenerative process (Tansey et al., 2007).

The beneficial effects of the inflammatory response include phagocytosis of debris, release of trophic factors, mobilization of neural precursors, axonal regeneration and remyelination (Geissmann et al., 2008; Nahrendorf et al., 2007; Schwartz and London, 2009). However, in order to produce its positive effects, the inflammatory response must be limited and resolved, ending with the restoration of immune homeostasis (Gronert, 2010). Under physiological conditions, endogenous factors down-regulate inflammation and provide a negative feedback that switches off the inflammatory response and prevents inflammatory-mediated damage (Griffiths et al., 2007). However, under sustained or prolonged inflammatory stimulation or with aging, these regulatory mechanisms become altered precipitating the neuronal damage (Frank et al., 2006; Stahel et al., 2009; Ye and Johnson, 2001). In particular, the altered inflammatory profiles characterized by increased production of pro-inflammatory mediators reported in aged microglia and the process of immune-senescence may be relevant for glaucoma and neurodegenerative pathologies having aging as main risk factor (Franceschi et al., 2000; Ma et al., 2013; Sheng et al., 1998; Sierra et al., 2007).

3. Neuroinflammation in glaucoma

In the eye the immune privilege is maintained by the presence of a specialized physical barrier, the blood-ocular barrier, which guarantees immune cell exclusion. However, as it has been described for the brain, the concept of immune privileged has evolved from the initial "immune-ignorance" to the idea that this privilege is aimed at maintaining a selective and tightly regulated immunological response, rather than entirely suppress it (Benhar et al., 2012; Niederkorn and Stein-Streilein, 2010; Stein-Streilein, 2008).

Astrocytes, Muller cells and microglia are the three types of resident glial cells in the retina and optic nerve (Vecino et al., 2015). Astrocytes are present in the unmyelinated optic nerve head, where they give mechanical and biochemical support to RGC axons, and in the retina where their somas are located in the ganglion cell layer (GCL) and nerve fiber layer (NFL); these *macroglial* cells are in contact with the superficial vascular plexus and extend their processes to the inner limiting membrane. Astrocytes play important roles in the homeostasis of retinal neurons supporting neuronal function (Butt et al., 2004). Moreover, their presence and distribution is strikingly associated with vasculature and, as the main producers of vascular endothelial growth factor (VEGF), astrocytes play important roles in retinal vascularization (Ozaki et al., 2000; Stone et al., 1995; Vecino et al., 2015).

Muller cells span the entire thickness of the retina having contact with all retinal cell type. This cell type is the major supportive glial cell for retinal neurons, representing 90% of the retinal glia, and plays important roles in several physiological processes that are fundamental for the proper function of the retina. Among others, Muller cells provide metabolic support and

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