Neuroinflammation mediated by microglial cells in the brain has been commonly associated with neurodegenerative diseases. Whether this microglia-mediated neuroinflammation is cause or consequence of neurodegeneration is still a matter of controversy. However, it is unequivocal that chronic neuroinflammation plays a role in disease progression and halting that process represents a potential therapeutic strategy. The neuromodulator adenosine emerges as a promising targeting candidate based on its ability to regulate microglial proliferation, chemotaxis, and reactivity through the activation of its G protein coupled A2A receptor (A2AR). This is in striking agreement with the ability of A2AR blockade to control several brain diseases. Retinal degenerative diseases have also been associated with microglia-mediated neuroinflammation, but the role of A2AR has been scarcely explored. This review aims to compare inflammatory features of Parkinson’s and Alzheimer’s diseases with glaucoma and diabetic retinopathy, discussing the therapeutic potential of A2AR in these degenerative conditions.

1. Introduction

1.1. Role of Microglia in Brain Physiology. In the central nervous system (CNS), microglial cells participate in innate immunity; microglia can respond to different types of signals, namely the presence of pathogens (extrinsic signals) or to intrinsic signals, namely diffusible mediators released by stressed neurons, astrocytes or microglia (reviewed in [1]). Although the present review mainly focuses on the contribution of microglia to the pathophysiology of neurodegeneration in the brain and the retina, any attempt to interfere with microglia in pathological conditions also needs to take into account the role of microglia in physiological conditions.

In the healthy brain, the majority of microglial cells exhibit a ramified phenotype, compatible with a surveillance function of the surrounding environment. This crucial sensor ability is supported by the constant extension and retraction of cellular processes [2, 3]. This dynamics is not random but instead instructed by increased neuronal activity, that activates pannexin-1 hemichannels, triggering the diffusion of signals, namely, ATP, that drive process motility towards that specific neuron [4]. The interconversion between the so-called “surveying” phenotype (considered more adequate, as compared to the old terminology “resting” phenotype) and the “alerted” phenotype can be driven either by external stimuli (e.g., pathogens) or by neural signals. The latter is achieved by direct neuron-microglia contact or by diffusible mediators (reviewed, e.g., in [1]). This activation of microglia drives some immediate responses that mainly consist in (1) production/release of rectifier mediators and (2) phagocytosis of neurons or subcellular components (mainly dendritic spines and synapses). Microglial phagocytosis of neurons or neuronal structures has been mostly studied in pathological conditions (e.g., [5–8]), but it also takes place in nonpathological conditions. In fact, it is a process of particular importance during neurodevelopment, as shown by Tremblay
and coworkers [9] in the visual system: light deprivation and the subsequent decrease in the workload of neuronal circuits involved in visual processing lead to the engulfment of synaptic elements by microglia. This physiological process, termed synaptic pruning, is regulated by the immune system; synapses and axons to be phagocytosed are labeled by the complement components C1q and C3, which prompt their selective recognition by microglial cells [10–12]. Synaptic pruning is crucial to normal brain wiring and function and any impairment of this process may impact on neurodevelopment. For instance, this was recently associated with deficits in synaptic transmission, which are paralleled by behavioral abnormalities characteristic of disorders of the autism spectrum and other neuropsychiatric conditions [13]. This process also occurs during adulthood, particularly in neurogenic niches of the brain, such as the hippocampus, where microglia phagocyte apoptotic newborn neurons [14].

Intriguingly, as part of their physiological role, microglia also actively shape their neuronal environment thanks to their ability to trigger neuronal death [15–17]. Again, such a role has a particular relevance during brain development, namely, during the first postnatal week, as heralded by the observation that microglia accumulate in regions of developmental cell death in the embryonic cerebral cortex [18]; furthermore, in the spinal cord, the cell death of motor neurons correlates temporally with the arrival of microglia [19].

In addition to their role in synaptic pruning, microglia also regulate synapse formation [20–22]. This function has been shown to be dependent on the production and release of mediators, such as brain-derived neurotrophic factor [20] or interleukin-10 (IL-10) [22], although other diffusible mediators are likely to be involved. This critical function of microglia must be strictly preserved in order to prevent neurodevelopmental deficits, as suggested by a recent in vitro study showing that activation of microglia by an inflammatory stimulus may impact on the presynaptic differentiation of immature neurons [25].

Microglial support to synapse formation/elimination is tightly associated with the newly recognized role of microglia as active partners in the transmission of information within synapses [24]. Thus, recent studies show that microglia also monitor the functional state of synapses and respond to changes in synaptic activity [25, 26]. Accordingly, the highly motile processes of microglia contact with synapses and regulate synaptic transmission in nonpathological conditions [9, 10, 27–30].

1.2. Role of Microglia in Retinal Physiology. In the adult retina, the presence of microglia has been described in several mammals species, including rabbits [31–33], mice [34], rats [31, 35, 36], monkeys [37, 38], and humans [39–41]. Microglial cells in the adult normal retina are mainly located in the inner vascularized regions, that is, the nerve fiber and ganglion cell layers and in plexiform layers, whereas they are scarce in the inner nuclear layer and absent in the outer nuclear layer (Figure 1).

In the healthy retina, microglial cells represent a self-renewing population of innate immune cells, which constantly survey their microenvironment, as occurs in the brain. Retinal microglia can also phagocyte pyknotic cells generated upon neural remodeling of the retina [42]. A more recent study performed in zebrafish showed that microglial cells not only have a “cleaning” role in the developing retina, but also are required for normal retinal growth and neurogenesis [43]. Microglia may also play a role in the formation of blood vessels in the developing retina, since microglia depletion during retinal development reduces vasularization, an effect restored by intravitreal injection of microglia [44]. This is in agreement with the origin of retinal microglial cells that originate from cells of mesodermal lineage [45] and populate the retina before vascularization and along with the onset of vasculogenesis [46].

1.3. A2AR Regulation of Microglia Physiology. Adenosine is a neuromodulator, which also exerts important functions in the immune-inflammatory system [47]. Microglial cells express all subtypes of adenosine receptors, A1, A2A, A2B, and A3 receptors [48]. Although a large body of evidence highlights the ability of A1 and A3 receptors to regulate microglia responses, such as proliferation, morphological phenotype, and release of mediators [49–52], particular attention has been paid to A2AR, considered to have a central role in the pathophysiology of degeneration [53–55].

It is claimed that A2AR modulation (both activation and blockade) interferes with microglia-mediated inflammation in degenerative conditions (see below). Of note, in
physiological conditions, important functions operated by microglia, namely, the release of mediators, such as trophic factors [56] or nitric oxide (NO) [57], as well as the extension and retraction of processes that govern the surveying activity of microglia [58], are apparently out of A2A R control, until a pathologic insult triggers a gain-of-function of A2A R [56, 57, 59, 60]. However, the milestone study by Davalos et al. [2] shows that the baseline motility of microglial processes in the healthy brain is governed by ATP (and prevented by ATP degradation), as occurs in pathological-like conditions. This observation raises the unanswered question whether the activation of A2A R by ATP-derived adenosine regulates the dynamics of microglial processes in physiological conditions.

1.4. Role of Microglia in Degenerative Conditions of the Brain.

The main physiologic roles operated by microglia (release of mediators that control synaptic transmission, synapse formation, and phagocytosis of cells or cellular elements) are strictly dependent upon their sensor ability. Any interference at this functional level may create conditions favoring the development of degenerative processes, which are bolstered by abnormal synaptic transmission, aberrant synapse formation and/or elimination, and abnormal phagocytosis (Figure 2). Therefore, the identification of molecular systems able to modulate microglial functions may help defining new pharmacological targets to interfere with the progression of neurodegenerative diseases. Indeed, microglia–driven neuroinflammation is associated with a broad spectrum of neurodegenerative diseases and has been more detailed in Alzheimer’s disease (AD) and Parkinson’s disease (PD).

The accumulation of misfolded β-amyloid-containing proteins (Abeta) and alpha-synuclein are histopathological hallmarks of established AD and PD, respectively [61–67]. Protein aggregates can directly exert neurotoxicity [68–70] and can trigger parallel maladaptive changes of glial cells; in fact, animal models of AD and PD and postmortem examination of the brain of AD or PD patients frequently reveal increased numbers of activated microglia in degenerated brain regions [71–76]. Moreover, in vivo studies using PET with a radiotracer for activated microglia in AD and PD patients have provided evidence for increased levels of activated microglia in brain regions that are affected by the disease [75–79]. Importantly, protein aggregates may be sufficient causative factors for microglial activation and release of inflammatory mediators [80], which, in turn, amplify neuroinflammation and further exacerbate neurodegeneration [73]. Such a scenario prompts the idea that microglia-induced neuroinflammation may play a critical role in the progression of neurodegenerative conditions [65–67, 81, 82].

Indeed, several microglia-derived inflammatory mediators have been shown to be involved in neuronal damage in neurodegenerative diseases. Thus, one possible causative factor for neuronal death in AD is Aβ-induced NO production by microglia [83]. Furthermore, Aβ and interferon-gamma (IFN-γ) can activate microglia to produce reactive nitrogen intermediates and tumor necrosis factor (TNF), contributing to neuronal degeneration observed in AD [84]. Additional proof-of-concept for the role of microglia in the progression of neuronal damage in AD was derived from the observation that drugs preventing microglial activation indeed delay the emergence of an AD-like phenotype in animal models [85]. Similarly, increased expression of inflammatory mediators is also found in PD animal models [51, 80, 86] and in postmortem PD brains [87, 88], including proinflammatory cytokines, such as IFN-γ, IL-1β, TNF, IL-2, and IL-6, released by microglia [89–91]. The microglial overactivation and the release of proinflammatory cytokines and reactive oxygen species (ROS) are associated with neuronal loss in PD [72, 73]; further evidence for the key role of these microglia-derived mediators in the evolution of neuronal damage in PD was obtained by showing that the inactivation of microglia-derived mediators counteracts neurodegeneration in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) animal model of PD [92–95].

In addition to the direct neurotoxic impact of these microglia-derived inflammatory mediators, the deregulation of the phagocytic activity of microglia also contributes to the progression of neuronal damage. This is heralded by the observations of an increased number of phagocytic microglia close to damaged neurons in PD [96, 97]; furthermore, blocking microglial activation attenuates neurodegeneration, further supporting the role of microglia in the evolution of the pathological process [98]. Increased phagocytosis of neuronal elements seems to be a selective process since in vitro studies have suggested that microglia may paradoxically reduce its ability to degrade Aβ-containing aggregates, and their intracellular accumulation leads to dysfunctional/dystrophic microglia [99–101]. In animal models of AD it has been shown in late stages of cerebral amyloidosis that the phagocytic capacity of microglia is impaired [102], and this impairment was described to accelerate pathology progression [103].

In summary, microglial functions, from the release of inflammatory mediators to the ability to phagocytose, are deregulated in neurodegenerative diseases. This implies that
the identification of regulatory systems able to rebalance microglial function may be of therapeutic interest to manage the progression of neurodegenerative diseases.

1.5. Control of Microglia-Driven Neuroinflammation by A2A R in Brain Diseases. The ability of adenosine and A2A R activation to control the activation of different inflammatory cell types has been consistently documented by different groups [47]. Likewise, several in vitro and in vivo studies clearly demonstrate that A2A R controls several facets of microglia dynamics [56–58, 104, 105], such as (1) the proliferation, (2) the levels of inflammatory enzymes such as cyclooxygenase-2, and (3) the synthesis and release of inflammatory mediators. Furthermore, studies carried out in several models of brain disorders have found that pharmacological blockade or genetic inactivation of A2A R affords a robust neuroprotection [53, 54], and increasing evidence suggests this neuroprotection involves the control of microglia-mediated neuroinflammation [54, 106, 107]. Furthermore, different brain insults triggering neuroinflammation also cause an upregulation of A2A R [56, 60], namely, in microglial cells [56, 57, 59, 108], which is in line with the described ability of cytokines to upregulate A2A R (reviewed by [53]). Finally, A2A R seem to have an additional ability to protect neurons from proinflammatory priming neurodegeneration [109, 110]. This has bolstered the interest to exploit A2A R as a promising pharmacological target to control the neuroinflammatory component of neurodegenerative diseases, allowing the slowdown of their evolution [47, 56, 106, 107].

The clinical interest of the adenosine modulation system in the control of memory dysfunction in AD first arose from epidemiological studies showing an inverse correlation between the consumption of moderate doses of caffeine (a nonselective adenosine receptor antagonist) and the deterioration of memory performance upon aging and AD [111]. This was in notable agreement with animal studies showing that the chronic consumption of caffeine reduces cognitive impairment and decreases Aβ levels in the brain of transgenic mouse models of AD [112–114], as well as in mice exposed to Aβ [104, 115], a purported causative factor of AD [64]. Animal studies were paramount to identify A2A R as the likely targets of caffeine [116], since the pharmacological or genetic blockade of A2A R mimics the neuroprotective effects of caffeine [104, 117]. In accordance with the involvement of neuroinflammatory features in AD, the exposure of rodents to lipopolysaccharide (LPS), which is present in the cell wall of gram-negative bacteria and used as a prototypical activator of microglia, triggers the activation of microglia, a proinflammatory status in the brain parenchyma, and deterioration of synaptic plasticity and memory performance [105]. Notably, this LPS-induced neuroinflammation can be prevented both by the caffeine [118] and by the selective blockade of A2A R [60], which abrogates the LPS-induced dampening of hippocampal synaptic plasticity, the purported neurophysiological basis of learning and memory [119]. Further supporting this role of microglial A2A R in AD, the analysis of postmortem human cortex from AD patients revealed an increased density of A2A R [60] that is more prominent in microglia [120].

As in AD, there is also solid evidence for a role of A2A R in the control of PD, as testified by the recent introduction of A2A R antagonists as coadjuvants in the management of PD [121]. Thus, A2A R antagonists improve PD symptoms in different rodent and primate models of the disease and also in PD patients enrolled in clinical trials (for a review see [122]). Besides the control of motor function, A2A R blockade also dampens microglial activation in the striatum [108] and substantia nigra [123] in animal models of PD. Furthermore, caffeine downregulates microglia-driven neuroinflammatory responses and decreases NO production in animal models of PD [124]. Although caffeine acts on both A1 R and A2A R, the neuroprotective properties of caffeine in PD are mediated through A2A R blockade [125, 126]. In fact, caffeine consumption has been associated with lower risk of PD in several case-control and cohort studies [127–132]. Interestingly, the association between coffee consumption and PD is strongest among subjects that slowly metabolize caffeine and are homozygous carriers of the CYPIA2 polymorphisms, the gene encoding for cytochrome P450 1A2 [133] which is the main enzyme involved in the metabolism of caffeine.

A recent ex vivo study (brain slices from MPTP-treated mice modeling PD) showed that a selective A2A R antagonist restores the ability of microglia to respond to tissue damage [134]. This A2A R-mediated control of neuroinflammation is argued to be critical for the neuroprotection afforded by A2A R blockade in PD since the inhibition of microglial function has been shown to be sufficient to decrease the dopaminergic neurodegeneration characteristic of PD.

These two examples of neurodegenerative diseases support the working hypothesis that the beneficial effects resulting from A2A R blockade may involve their ability to attenuate microglial activation and associated chronic neuroinflammatory status, which would interrupt the vicious cross amplifying cycle of degeneration and inflammation leading to a slower development of neurodegenerative disorders (Figure 3).

1.6. Neuroinflammation Is a Common Feature between Retinal and Brain Degenerative Diseases. The combined effect of an ageing population and increasing life expectancy will increase the prevalence of chronic diseases [135], which encompass not only neurodegenerative brain diseases, but also retinal degenerative conditions amongst others. Indeed, the demographic evolution, with an increasing elderly population in western countries, exponentially augments the number of people at risk of age-related visual impairment caused by age-related retinal degenerative diseases [136]. Glaucoma and diabetic retinopathy are leading causes of blindness worldwide. Glaucoma is the second cause of irreversible blindness [137], affecting 70 million people worldwide and approximately 2% of the population over the age of 40 [138]. Diabetic retinopathy is a frequent complication of diabetes and may lead to blindness, making it one of the most feared complications of diabetes. Indeed, diabetic retinopathy is the leading
1. Micronesia and neuroinflammation in the brain/retina. Schematic representation of the main inflammatory responses mediated by microglial cells (in yellow) in neurodegenerative conditions. Environment surveillance allows the detection of "pathological" events affecting neurons (in blue-purple); note that appropriate detection of danger signals may also be compromised under these conditions; one of the microglial changes consists in the upregulation of the expression/density of A2A R, as described in several degenerative disorders (1), usually paralleled by morphologic changes and by the release of inflammatory mediators (red circles), both anti- and proinflammatory molecules, that may impact on synaptic transmission, ultimately leading to synaptotoxicity (2); the ability of microglia to phagocytose subcellular components of damaged neurons or protein aggregates, typically present in some degenerative diseases, may also be impaired, further amplifying the cascade of events that lead to cell death/degeneration (3).

1.7. Glaucoma Has a Neuroinflammatory Component. Glaucoma is defined as a group of ocular disorders of multifactorial etiology characterized by progressive optic neuropathy [143] and gradual loss of retinal ganglion cells and optic nerve (retinal ganglion cell axons) damage. Elevated intraocular pressure (IOP) is one of the major risk factors for developing glaucoma or glaucomatous neuropathy [144]. The current therapeutic approach in glaucoma is focused on lowering IOP by pharmacological means, surgically, or with laser treatment. However, patients continue to lose vision despite successful IOP control, and it is becoming clear that the exclusive management of IOP is not sufficient, and neuroprotection of retinal ganglion cells has been proposed as a potential alternative therapy [145].

Several studies have reported that the progressive degeneration of optic nerve axons and retinal ganglion cells in glaucoma is accompanied by chronic alterations in structural and functional characteristics of glial cells in the optic nerve head and retina [146, 147], where an abnormal microglial reactivity and redistribution take place [148]. TNF, IL-6, and IL-18 levels are increased in the retina and optic nerve head in both glaucomatous patients and animal models of glaucoma [149–151] and recent studies demonstrate that microglial activation is an early event in experimental models of glaucoma, which coincides with the onset of RGC death, potentially contributing to disease onset and/or progression [152–154]. Also, the treatment with minocycline, a tetracycline derivative known to reduce microglial activation [155], was able to improve retinal ganglion cell axonal transport and integrity in a mouse model of glaucoma [156].

1.8. Diabetic Retinopathy: A Low-Grade Inflammatory Disease. Diabetic retinopathy is one of the most common complications of diabetes and the most frequent cause of new cases of blindness among adults aged 20–74 years. After 20 years of diabetes, nearly all patients with type 1 and more than 60% of patients with type 2 diabetes have some degree of retinopathy [157]. Diabetic retinopathy has been considered a microvascular disease, but growing evidence demonstrates that retinal neurodegeneration also occurs [158–160], and
diabetic retinopathy is now more accurately defined as a neurovascular disease.

Diabetic retinopathy exhibits characteristics of a chronic inflammatory process: increased levels of cytokines, such as IL-1β, IL-6, and TNF, have been found in the vitreous fluid of diabetic patients [161–163]; retinal TNF levels are also increased in diabetic patients, particularly in those with proliferative diabetic retinopathy [164–166]. The inflammatory profile of diabetic retinopathy has been confirmed in animal models of diabetes, where an increase was found in the levels of IL-1β [167–170] and TNF [170–172] in the retina. Therefore, the role of inflammation is unequivocal in diabetic retinopathy, from the leukocyte adhesion [173, 174] to the increase in inflammatory mediators, such as TNF, which exerts a crucial role in blood retinal barrier breakdown [175], as well as the death of retinal neurons [176]. As occurs in neurodegenerative brain diseases, microglial activation in the retina is also present in different stages of human diabetic retinopathy [177] and further reported in animals models of type 1 [170, 178–180] and type 2 [181] diabetes.

1.9. Is There a Role for $\Delta_2$AR in Retinal Degenerative Diseases?

Retinal ischemia is a common cause of visual impairment and blindness (reviewed in [182]). Retinal degeneration after ischemia-reperfusion injury by transient elevation of IOP in rats exhibits an extensive damage at the level of the retinal ganglion cell layer [183], similarly to that reported in human glaucoma [184]. Therefore, IOP-induced retinal ischemia has been extensively used as an animal model of acute glaucoma [185], in which activation of microglia has also been observed [36]. The role of $\Delta_2$AR in retinal ischemia-reperfusion injury is still controversial. On one hand, the treatment with a selective $\Delta_2$AR antagonist protects retinal function and structure in a model of retinal ischemia [186, 187]. On the other hand, it was reported that administration of an $\Delta_2$AR agonist prevents retinal thinning induced by ischemia-reperfusion damage [188].

Traumatic optic neuropathy is an important cause of severe vision loss in 0.5 to 5% of patients with closed head trauma [189]. Trauma is known to cause immediate mechanical damage to the axons of retinal ganglion cells, leading to degeneration. The death of retinal ganglion cells after optic nerve damage seems to be related to the local production of ROS and inflammatory mediators from activated microglial cells [190]. Increased phagocytic and proliferative microglia have been reported after optic nerve injury [191–193]. In the optic nerve crush injury mouse model, an important experimental disease model for traumatic optic neuropathy, a selective $\Delta_2$AR agonist decreased microglial activation, retinal cell death, and release of ROS and proinflammatory cytokines [190]. Moreover, levels of TNF and Iba-1 (a marker of cells from the myeloid lineage, including microglia) are increased in $\Delta_2$AR-knockout mice with optic nerve crush. In a different model of retinal degeneration, diabetic retinopathy, it was recently shown that $\Delta_2$AR mRNA transcripts and protein levels increase in the retina of type 1 diabetes models and also in retinal cell cultures exposed to elevated glucose concentration, used to mimic hyperglycemic conditions [194, 195]. $\Delta_2$AR-knockout diabetic mice exhibit increased cell death and TNF levels as compared with diabetic wild-type mice [179]. Accordingly, the administration of a selective $\Delta_2$AR agonist resulted in opposite effects upon cell death and TNF levels [179].

Experiments performed in vitro emphasize the controversial role played by $\Delta_2$AR in the control of retinal neuroinflammation. While some authors reported that the activation of $\Delta_2$AR attenuates LPS-induced release of TNF in retinal microglia [190], others found that $\Delta_2$AR blockade prevents LPS-induced increase in NO [196]. Moreover, $\Delta_2$AR blockade inhibits the LPS-induced increase in TNF expression and phagocytosis. In a more complex system, the retinal organotypic culture, $\Delta_2$AR blockade inhibits the expression of inducible NO synthase [196].

In summary, it remains to be clarified whether $\Delta_2$AR activation or blockade is the best approach to pharmacologically control neuroinflammation in the retina. This dual neuroprotective ability of $\Delta_2$AR modulation seems to be related with the specific inflammatory profile of different pathologies or pathologic conditions, as well as with the temporal window of neuroinflammation where the exposure to $\Delta_2$AR agonists or antagonists occurs. Although the controversy exists, most studies in brain pathology point towards a neuroprotective effect of $\Delta_2$AR blockade, in line with the ability of selective and nonselective $\Delta_2$AR antagonists to decrease most microglial functions.

2. Concluding Remarks

Brain degenerative diseases, such as AD and PD, are associated with microglial activation and chronic neuroinflammation. In both pathologies, the blockade of $\Delta_2$AR emerges as a candidate mechanism of neuroprotection, through the control of microglial reactivity. Glaucma and diabetic retinopathy are retinal degenerative diseases, in which neuroinflammation also plays a crucial role. In the retina, microglial cells are also equipped with $\Delta_2$AR. Therefore, it is plausible to assume that $\Delta_2$AR modulation may also have a potential protective effect upon inflammation underlying degenerative processes of the retina (Figure 4). It remains to be clarified whether $\Delta_2$AR modulation has a net positive effect in the control of clinical features and progression of retinal degenerative diseases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work was supported by the Foundation for Science and Technology and COMPETE-FEDER (SFRH/BPD/86830/2012, SFRH/BPD/63013/2009, PTDC/BIM-MEC/0913/2012,
Figure 4: Cellular and molecular commonalities between the brain and the retina. Scheme identifying main microglial functions under the control of A<sub>2A</sub>R: release of inflammatory mediators and cellular proliferation. It remains to clarify if process extension/retraction (which supports the homeostatic surveying role of microglia), phagocytosis, and cellular migration are directly regulated by A<sub>2A</sub>R modulation (question marks). A<sub>2A</sub>R modulation is proposed as a promising pharmacological tool in the control of the chronic inflammatory process underlying degenerative conditions of the retina, based on similarities with microglia-mediated inflammation in brain disorders.

References

[1] K. Saijo and C. K. Glass, "Microglial cell origin and phenotypes in health and disease," *Nature Reviews Immunology*, vol. 11, no. 11, pp. 775–787, 2011.

[2] D. Davalos, J. Grutzendler, G. Yang et al., "ATP mediates rapid microglial response to local brain injury in vivo," *Nature Neuroscience*, vol. 8, no. 6, pp. 752–758, 2005.

[3] A. Nimmerjahn, F. Kirchhoff, and F. Helmchen, "Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo," *Science*, vol. 308, no. 5726, pp. 1314–1318, 2005.

[4] Y. Li, X. Du, C. Liu, Z. Wen, and J. Du, "Reciprocal regulation between resting microglial dynamics and neuronal activity in vivo," *Developmental Cell*, vol. 23, no. 6, pp. 1189–1202, 2012.

[5] H. Wake, A. J. Moorhouse, S. Jinno, S. Kohsaka, and J. Nabekura, "Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals," *The Journal of Neuroscience*, vol. 29, no. 13, pp. 3974–3980, 2009.

[6] S. M. Lu, M. E. Tremblay, I. L. King et al., "HIV-1 Tat-induced microgliosis and synaptic damage via interactions between peripheral and central myeloid cells," *PLoS ONE*, vol. 6, no. 9, Article ID e23915, 2011.

[7] A. D. Kraft, L. S. Kaltenbach, D. C. Lo, and G. J. Harry, "Activated microglia proliferate at neurites of mutant huntingtin-expressing neurons," *Neurobiology of Aging*, vol. 33, no. 3, pp. 621.e17–621.e33, 2012.

[8] D. Chugh, P. Nilsson, S. A. Afjei, A. Bakochi, and C. T. Ekdahl, "Brain inflammation induces post-synaptic changes during early synapse formation in adult-born hippocampal neurons," *Experimental Neurology*, vol. 250, pp. 176–188, 2013.

[9] M. Tremblay, R. L. Lowery, and A. K. Majewska, "Microglial interactions with synapses are modulated by visual experience," *PLoS Biology*, vol. 8, no. 11, Article ID e1000527, 2010.

[10] R. C. Paolicelli, G. Bolasco, F. Pagani et al., "Synaptic pruning by microglia is necessary for normal brain development," *Science*, vol. 333, no. 6048, pp. 1456–1458, 2011.

[11] B. Linnartz, J. Kopatz, A. J. Tenner, and H. Neumann, "Sialic acid on the neuronal glycopipid prevents complement c1 binding and complement receptor-3-mediated removal by microglia," *The Journal of Neuroscience*, vol. 32, no. 3, pp. 946–952, 2012.

[12] D. P. Schafer, E. K. Lehrman, A. G. Kautzman et al., "Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner," *Neuron*, vol. 74, no. 4, pp. 691–705, 2012.

[13] Y. Zhan, R. C. Paolicelli, F. Sforazzini et al., "Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior," *Nature Neuroscience*, vol. 17, no. 3, pp. 400–406, 2014.

[14] A. Sierra, J. M. Encinas, J. J. P. Deudero et al., "Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis," *Cell Stem Cell*, vol. 7, no. 4, pp. 483–495, 2010.

[15] J. L. Marin-Teva, I. Dusart, C. Colin, A. Gervais, N. Van Rooijen, and M. Mallat, "Microglia promote the death of developing Purkinje cell," *Neuron*, vol. 41, no. 4, pp. 535–547, 2004.

[16] S. Wakselman, C. Béchade, A. Roumier, D. Bernard, A. Triller, and A. Bessis, "Developmental neuronal death in hippocampus requires the microglial CD11b integrin and DAP12 immunoreceptor," *The Journal of Neuroscience*, vol. 28, no. 32, pp. 8138–8143, 2008.

[17] C. M. Tyler and L. M. Boulanger, "Complement-mediated microglial clearance of developing retinal ganglion cell axons," *Neuron*, vol. 74, no. 4, pp. 597–599, 2012.
[52] J. Y. Lee, B. S. Jhun, Y. T. Oh et al., “Activation of adenosine A3 receptor suppresses lipopolysaccharide-induced TNF-α production through inhibition of PI 3-kinase/Akt and NF-κB activation in murine BV2 microglial cells,” *Neuroscience Letters*, vol. 396, no. 1, pp. 1–6, 2006.

[53] R. A. Cunha, “Neuroprotection by adenosine in the brain: from A1 receptor activation to A2A receptor blockade,” *Purinergic Signalling*, vol. 1, no. 2, pp. 111–134, 2005.

[54] C. V. Gomes, M. P. Kaster, A. R. Tomé, P. M. Agostinho, and R. A. Cunha, “Adenosine receptors and brain diseases: neuroprotection and neurodegeneration,” *Biochimica et Biophysica Acta*, vol. 1808, no. 5, pp. 1380–1399, 2011.

[55] J. Chen, P. K. Sonsalla, F. Pedata et al., “Adenosine A2A receptors and brain injury: broad spectrum of neuroprotection, multifaceted actions and “fine tuning” modulation,” *Progress in Neurobiology*, vol. 83, no. 5, pp. 310–331, 2007.

[56] C. Gomes, R. Ferreira, J. George et al., “Activation of microglial cells triggers a release of brain-derived neurotrophic factor (BDNF) inducing their proliferation in an adenosine A2A receptor-dependent manner: A2A receptor blockade prevents BDNF release and proliferation of microglia,” *Journal of Neuroinflammation*, vol. 10, article 16, 2013.

[57] J. Saura, E. Angulo, A. Ejarque et al., “Adenosine A2A receptor stimulation potentiates nitric oxide release by activated microglia,” *Journal of Neurochemistry*, vol. 95, no. 4, pp. 919–929, 2005.

[58] A. G. Orr, A. L. Orr, X. Li, R. E. Gross, and S. F. Traynelis, “Adenosine A2A receptor mediates microglial process retraction,” *Nature Neuroscience*, vol. 12, no. 7, pp. 872–878, 2009.

[59] S. S. Dai, Y. G. Zhou, W. Li et al., “Local glutamate level dictates adenosine A2A receptor regulation of neuroinflammation and traumatic brain injury,” *The Journal of Neuroscience*, vol. 30, no. 16, pp. 5802–5810, 2010.

[60] J. L. Albasanz, S. Perez, M. Barrachina, I. Ferrer, and M. Martin, “Up-regulation of adenosine receptors in the frontal cortex in Alzheimer’s disease,” *Brain Pathology*, vol. 18, no. 2, pp. 211–219, 2008.

[61] D. M. Holtzman, J. C. Morris, and A. M. Goate, “Alzheimer’s disease: the challenge of the second century,” *Science Translational Medicine*, vol. 3, no. 77, Article ID 77sr1, 2011.

[62] L. Buée, T. Bussière, V. Buée-Scherrer, A. Delacourte, and P. R. Hof, “Tau protein isoforms, phosphorylation and role in neurodegenerative disorders,” *Brain Research Reviews*, vol. 33, no. 1, pp. 95–130, 2000.

[63] T. F. Gendron and L. Petrucelli, “The role of tau in neurodegeneration,” *Molecular Neurodegeneration*, vol. 4, no. 1, article 13, 2009.

[64] D. J. Selkoe and D. Schenk, “Alzheimer’s disease: molecular understanding predicts amyloid-based therapeutics,” *Annual Review of Pharmacology and Toxicology*, vol. 43, pp. 545–584, 2003.

[65] P. L. McGeer and E. G. McGeer, “Glial reactions in Parkinson’s disease,” *Movement Disorders*, vol. 23, no. 4, pp. 474–483, 2008.

[66] E. C. Hirsch and S. Hunot, “Neuroinflammation in Parkinson’s disease: a target for neuroprotection?” *The Lancet Neurology*, vol. 8, no. 4, pp. 382–397, 2009.

[67] T. Nagatsu and M. Sawada, “Inflammatory process in Parkinson’s disease: role for cytokines,” *Current Pharmaceutical Design*, vol. 11, no. 8, pp. 999–1016, 2005.

[68] E. Gómez-Tortosa, K. Newell, M. C. Irizarry, M. Albert, J. H. Growdon, and B. T. Hyman, “Clinical and quantitative pathologic correlates of dementia with Lewy bodies,” *Neurology*, vol. 53, no. 6, pp. 1284–1291, 1999.

[69] E. Masliiah, E. Rockenstein, I. Veinbergs et al., “Dopaminergic loss and inclusion body formation in α-synuclein mice; implications for neurodegenerative disorders,” *Science*, vol. 287, no. 5456, pp. 1265–1269, 2000.

[70] B. A. Yankner and T. Lu, “Amyloid β-protein toxicity and the pathogenesis of Alzheimer disease,” *The Journal of Biological Chemistry*, vol. 284, no. 8, pp. 4755–4759, 2009.

[71] P. L. McGeer, S. Itagaki, H. Tago, and E. G. McGeer, “Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR,” *Neuroscience Letters*, vol. 79, no. 1-2, pp. 195–200, 1987.

[72] P. L. McGeer, S. Itagaki, B. E. Boyes, and E. G. McGeer, “Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson’s and Alzheimer’s disease brains,” *Neurology*, vol. 38, no. 8, pp. 1285–1291, 1988.

[73] S. V. More, H. Kumar, I. S. Kim, S. Y. Song, and D. K. Choi, “Cellular and molecular mediators of neuroinflammation in the pathogenesis of Parkinson’s disease,” *Mediators of Inflammation*, vol. 2013, Article ID 952375, 12 pages, 2013.

[74] X. Su, H. J. Federoff, and K. A. Maguire-Zeiss, “Mutant α-synuclein overexpression mediates early proinflammatory activity,” *Neurotoxicity Research*, vol. 16, no. 3, pp. 238–254, 2009.

[75] Y. Ouchi, E. Yoshikawa, Y. Sekine et al., “Microglial activation and dopamine terminal loss in early Parkinson’s disease,” *Annals of Neurology*, vol. 57, no. 2, pp. 168–175, 2005.

[76] A. Gerhard, N. Pavese, G. Hotton et al., “In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson’s disease,” *Neurobiology of Disease*, vol. 21, no. 2, pp. 404–412, 2006.

[77] A. Schuitemaker, M. A. Krogholler, R. Boellaard et al., “Microglial activation in Alzheimer’s disease: an [(R)-[11C]PK11195 positron emission tomography study,” *Neurobiology of Aging*, vol. 34, no. 1, pp. 128–136, 2013.

[78] A. Okello, P. Edison, H. A. Archer et al., “Microglial activation and amyloid deposition in mild cognitive impairment: a PET study,” *Neurology*, vol. 72, no. 1, pp. 56–62, 2009.

[79] P. Edison, H. A. Archer, A. Gerhard et al., “Microglia, amyloid, and cognition in Alzheimer’s disease: an [(1)C](R)PK1195-PET and [(1)C]PIB-PET study,” *Neurobiology of Disease*, vol. 32, no. 3, pp. 412–419, 2008.

[80] W. Zhang, T. Wang, Z. Pei et al., “Aggregated α-synuclein activates microglia: a process leading to disease progression in Parkinson’s disease,” *The FASEB Journal*, vol. 19, no. 6, pp. 533–542, 2005.

[81] C. K. Combs, D. E. Johnson, J. C. Karlo, S. B. Cannady, and G. E. Landreth, “Inflammatory mechanisms in Alzheimer’s disease: inhibition of β-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARγ agonists,” *Journal of Neuroscience*, vol. 20, no. 2, pp. 558–567, 2000.

[82] L. Qin, Y. Liu, C. Cooper, B. Liu, B. Wilson, and J. Hong, “Microglia enhance β-amyloid peptide-induced toxicity in cortical and mesencephalic neurons by producing reactive oxygen species,” *Journal of Neurochemistry*, vol. 83, no. 4, pp. 973–983, 2002.

[83] M. Ii, M. Sunamoto, K. Ohnishi, and Y. Ichimori, “β-Amyloid protein toxicity and the pathological role of nitric oxide production from microglial cells and neurotoxicity,” *Brain Research*, vol. 720, no. 1-2, pp. 93–100, 1996.

[84] L. Meda, M. A. Cassatella, G. I. Szendrei et al., “Activation of microglial cells by β-amyloid protein and interferon-γ,” *Nature*, vol. 374, no. 6523, pp. 647–650, 1995.
NADPH oxidase-mediated oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson’s disease,” Proceedings of the National Academy of Sciences of the United States of America, vol. 100, no. 10, pp. 6145–6150, 2003.

S. Hunot, F. Boissière, B. Faucheux et al., “Nitric oxide synthase and neuronal vulnerability in Parkinson’s disease,” Neuroscienece, vol. 72, no. 2, pp. 355–363, 1996.

C. Knott, G. Stern, and G. P. Wilkin, “Inflammatory regulators in Parkinson’s disease: iNOS, lipocortin-1, and cyclooxygenases-1 and -2,” Molecular and Cellular Neuroscience, vol. 16, no. 6, pp. 724–739, 2000.

R. Lee Mosley, E. J. Benner, I. Kadiu et al., “Neuroinflammation, oxidative stress, and the pathogenesis of Parkinson’s disease,” Clinical Neuroscience Research, vol. 6, no. 5, pp. 261–281, 2006.

A. L. de Lella Ezcurra, M. Chertoff, C. Ferrari, M. Graciarena, and D. Wu, “Selective COX-2 inhibition prevents progressive dopamine neuron degeneration in a rat model of Parkinson’s disease,” Journal of Neuroinflammation, vol. 3, no. 3, pp. 630–640, 2010.

T. Nagatsu, M. Mogi, H. Ichinose, and A. Togari, “Changes in cytokines and neurotrophins in Parkinson’s disease,” Journal of Neural Transmission, Supplement, no. 60, pp. 277–290, 2000.

P. Teismann, K. Tieu, D. K. Choi et al., “Cyclooxygenase-2 is instrumental in Parkinson’s disease neurodegeneration,” Proceedings of the National Academy of Sciences of the United States of America, vol. 100, no. 9, pp. 5473–5478, 2003.

S. Hunot, M. Vila, P. Teismann et al., “JNK-mediated induction of cyclooxygenase 2 is required for neurodegeneration in a mouse model of Parkinson’s disease,” Proceedings of the National Academy of Sciences of the United States of America, vol. 101, no. 2, pp. 665–670, 2004.

R. Sánchez-Pernaute, A. Ferrere, O. Cooper, M. Yu, A. Brownell, and O. Isacson, “Selective COX-2 inhibition prevents progressive dopamine neuron degeneration in a rat model of Parkinson’s disease,” Journal of Neuroinflammation, vol. 1, article 6, 2004.

G. T. Liberatore, V. Jackson-Lewis, S. Vukosavic et al., “Inducible nitric oxide synthase stimulates dopaminergic neurodegeneration in the MPTP model of Parkinson disease,” Nature Medicine, vol. 5, no. 12, pp. 1403–1409, 1999.

K. Imamura, N. Hishikawa, M. Sawada, T. Nagatsu, M. Yoshida, and Y. Hashizume, “Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson’s disease brains,” Acta Neuropathologica, vol. 106, no. 6, pp. 518–526, 2003.

E. Croisier, L. B. Moran, D. T. Dexter, R. K. B. Pearce, and M. B. Graeber, “Microglial inflammation in the parkinsonian substantia nigra: relationship to α-synuclein deposition,” Journal of Neuroinflammation, vol. 2, article 14, 2005.

D. C. Wu, V. Jackson-Lewis, M. Vila et al., “Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease,” Journal of Neuroscience, vol. 22, no. 5, pp. 1763–1771, 2002.

D. M. Paresce, H. Chung, and F. R. Maxfield, “Slow degradation of aggregates of the Alzheimer’s disease amyloid β protein by microglial cells,” The Journal of Biological Chemistry, vol. 272, no. 46, pp. 29390–29397, 1997.

D. G. Walker and L.-F. Lue, “Investigations with cultured human microglia on pathogenic mechanisms of Alzheimer’s disease and other neurodegenerative diseases,” Journal of Neuroscience Research, vol. 81, no. 3, pp. 412–425, 2005.

A. Majumdar, D. Cruz, N. Asamoa et al., “Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils,” Molecular Biology of the Cell, vol. 18, no. 4, pp. 1490–1496, 2007.

G. Krabbe, A. Halle, V. Matyash et al., “Functional impairment of microglia coincides with Beta-amyloid deposition in mice with Alzheimer-like pathology,” PLoS ONE, vol. 8, no. 4, Article ID e60921, 2013.

J. El Khoury, M. Toft, S. E. Hickman et al., “Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease,” Nature Medicine, vol. 13, no. 4, pp. 432–438, 2007.

P. M. Canas, L. O. Porciúncula, G. M. A. Cunha et al., “Adenosine A2A receptor blockade prevents synaptotoxicity and memory dysfunction caused by β-amyloid peptides via p38 mitogen-activated protein kinase pathway,” Journal of Neuroscience, vol. 29, no. 47, pp. 14741–14751, 2009.

N. Rebola, A. P. Simões, P. M. Canas et al., “Adenosine A2A receptors control neuroinflammation and consequent hippocampal neuronal dysfunction,” Journal of Neurochemistry, vol. 117, no. 1, pp. 100–111, 2011.

L. Minghetti, A. Greco, R. L. Potenza et al., “Effects of the adenosine A2A receptor antagonist SCH 58621 on cyclooxygenase-2 expression, glial activation, and brain-derived neurotrophic factor availability in a rat model of striatal neurodegeneration,” Journal of Neuropathology and Experimental Neurology, vol. 66, no. 5, pp. 363–371, 2007.

F. Di Virgilio, S. Ceruti, P. Bramanti, and M. P. Abbracchio, “Purinergic signalling in inflammation of the central nervous system,” Trends in Neurosciences, vol. 32, no. 2, pp. 79–87, 2009.

L. Yu, H. Shen, J. F. Coelho et al., “Adenosine A2A receptor antagonists exert motor and neuroprotective effects by distinct cellular mechanisms,” Annals of Neurology, vol. 63, no. 3, pp. 338–346, 2008.

A. P. Simões, J. A. Duarte, F. Agasse et al., “Blockade of adenosine A2A receptors prevents interleukin-1β-induced exacerbation of neuronal toxicity through a p38 mitogen-activated protein kinase pathway,” Journal of Neuroinflammation, vol. 9, article 204, 2012.

T. W. Stone and W. M. H. Behan, “Interleukin-1β but not tumor necrosis factor-α potentiates neuronal damage by quinolinic acid: protection by an adenosine A2A receptor antagonist,” Journal of Neuroscience Research, vol. 85, no. 5, pp. 1077–1085, 2007.

B. B. Fredholm, J. F. Chen, R. A. Cunha, P. Svenningsson, and J. M. Vaugeois, “Adenosine and brain function,” Annals of Neurology, vol. 63, no. 4, pp. 338–346, 2008.

G. A. Locascio, J. F. Chen, R. A. Cunha, and J. M. Vaugeois, “Adenosine and brain function,” International Review of Neurobiology, vol. 93, pp. 191–205, 2007.

G. W. Arendash, T. Mori, C. Cao et al., “Caffeine reverses cognitive impairment and decreases brain amyloid-β levels in aged Alzheimer’s disease mice,” Journal of Alzheimer’s Disease, vol. 17, no. 3, pp. 661–680, 2009.

C. Cao, J. R. Cirrito, X. Lin et al., “Caffeine suppresses amyloid-β levels in plasma and brain of Alzheimer’s disease transgenic mice,” Journal of Alzheimer’s Disease, vol. 17, no. 3, pp. 681–697, 2009.
[114] Y. F. Chu, W. H. Chang, R. M. Black et al., "Crude caffeine reduces memory impairment and amyloid β(1–42) levels in an Alzheimer's mouse model," Food Chemistry, vol. 135, no. 3, pp. 2095–2102, 2012.

[115] O. P. Dall’Igna, P. Fett, M. W. Gomes, D. O. Souza, R. A. Cunha, and D. R. Lara, "Caffeine and adenosine A2A receptor antagonists prevent β-amloid (25–35)-induced cognitive deficits in mice," Experimental Neurology, vol. 205, no. 1, pp. 241–245, 2007.

[116] R. A. Cunha and P. M. Agostinho, "Chronic caffeine consumption prevents memory disturbance in different animal models of memory decline," Journal of Alzheimer's Disease, vol. 20, supplement 1, pp. S95–S116, 2010.

[117] O. P. Dall’Igna, L. O. Porciuncula, D. O. Souza, R. A. Cunha, and D. R. Lara, "Neuroprotection by caffeine and adenosine A2A receptor blockade of beta-amloid neurotoxicity," British Journal of Pharmacology, vol. 138, no. 7, pp. 1207–1209, 2003.

[118] H. M. Brothers, Y. Marchalant, and G. L. Wenk, "Caffeine attenuates lipopolysaccharide-induced neuroinflammation," Neurosciences Letters, vol. 480, no. 2, pp. 97–100, 2010.

[119] M. A. Lynch, "Long-term potentiation and memory," Physiological Reviews, vol. 84, no. 1, pp. 87–136, 2004.

[120] A. Angulo, V. Casadó, J. Mallol et al., "At adenosine receptors accumulate in neurodegenerative structures in Alzheimer disease and mediate both amyloid precursor protein processing and tau phosphorylation and translocation," Brain Pathology, vol. 13, no. 4, pp. 440–451, 2003.

[121] W. Chen, H. Wang, H. Wei, and S. Gu, "Istradefylline, an adenosine A2A receptor antagonist, for patients with Parkinson's disease: a meta-analysis," Journal of the Neurological Sciences, vol. 324, no. 1, pp. 21–28, 2013.

[122] M. Morelli, A. R. Carta, and P. Jenner, "Adenosine A2A receptors and Parkinson's disease," Handbook of Experimental Pharmacology, vol. 193, pp. 589–615, 2009.

[123] M. Pierri, E. Vaudano, T. Sager, and U. Englund, "KW-6002 receptor antagonists prevent memory disturbance in different animal models of memory decline," Journal of Alzheimer's Disease, vol. 20, supplement 1, pp. S221–S238, 2010.

[124] R. Liu, X. Guo, Y. Park et al., "Caffeine intake, smoking, and risk of parkinson disease in men and women," American Journal of Epidemiology, vol. 175, no. 11, pp. 1200–1207, 2012.

[125] M. van der Mark, P. C. Nijssen, J. Vlaanderen et al., "A case-control study of the protective effect of alcohol, coffee, and cigarette consumption on Parkinson disease risk: time-since-cessation modifies the effect of tobacco smoking," PloS ONE, vol. 9, no. 4, Article ID e95297, 2014.

[126] K. Sääksjärvi, P. Knekt, H. Rissanen, M. A. Laaksonen, A. Reunanen, and S. Männistö, "Prospective study of coffee consumption and risk of Parkinson's disease," European Journal of Clinical Nutrition, vol. 62, no. 7, pp. 908–915, 2008.

[127] G. W. Ross, R. D. Abbott, H. Petrovitch et al., "Association of coffee and caffeine intake with the risk of Parkinson disease," Journal of the American Medical Association, vol. 283, no. 20, pp. 2674–2679, 2000.

[128] R. A. Popat, S. K. Van Den Eeden, C. M. Tanner et al., "Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease," European Journal of Nutrition, vol. 18, no. 5, pp. 756–765, 2011.

[129] S. Gyoneva, L. Shapiro, C. Lazo et al., "Adenosine A2A receptor antagonism reverses inflammation-induced impairment of microglial process extension in a model of Parkinson's disease," Neurobiology of Disease, vol. 67, pp. 191–202, 2014.

[130] World Population Ageing 2013, Department of Economic and Social Affairs, Population Division, New York, NY, USA, 2013.

[131] G. Dagnelie, "Age-related psychophysical changes and low vision," Investigative Ophthalmology & Visual Science, vol. 54, no. 14, pp. ORSF88–ORSF93, 2013.

[132] S. Resnikoff, D. Pascolini, D. Etya'ale et al., "Global data on visual impairment in the year 2002," Bulletin of the World Health Organization, vol. 82, no. 11, pp. 844–851, 2004.

[133] W. Cheung, L. Guo, and M. F. Cordeiro, "Neuroprotection in glaucoma: drug-based approaches," Optometry and Vision Science, vol. 85, no. 6, pp. E406–E416, 2008.

[134] International Diabetes Federation, IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium, 6th edition, 2013.

[135] S. J. McKinnon, "The cell and molecular biology of glaucoma: common neurodegenerative pathways and relevance to glaucoma," Investigative Ophthalmology and Visual Science, vol. 53, no. 5, pp. 2485–2487, 2012.

[136] J. M. Sivak, "The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease," Investigative Ophthalmology and Visual Science, vol. 54, no. 1, pp. 871–880, 2013.

[137] G. I. Liou, J. A. Auchampach, C. J. Hillard et al., "Mediation of cannabinoid anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor," Investigative Ophthalmology and Visual Science, vol. 49, no. 12, pp. 5526–5531, 2008.

[138] R. J. Casson, G. Chidlow, J. P. M. Wood, J. G. Crowston, and I. Goldberg, "Definition of glaucoma: clinical and experimental concepts," Clinical and Experimental Ophthalmology, vol. 40, no. 4, pp. 341–349, 2012.

[139] T. Kersey, C. I. Clement, P. Bloom, and M. F. Cordeiro, "New trends in glaucoma risk, diagnosis & management," Indian Journal of Medical Research, vol. 137, no. 4, pp. 659–668, 2013.

[140] M. F. Cordeiro and L. A. Levin, "Clinical evidence for neuroprotection in glaucoma," American Journal of Ophthalmology, vol. 152, no. 5, pp. 715–716, 2011.

[141] G. Tezel, "The role of glia, mitochondria, and the immune system in glaucoma," Investigative Ophthalmology and Visual Science, vol. 50, no. 3, pp. 1001–1012, 2009.
A. Baltmr, J. Duggan, S. Nizari, T. E. Salt, and M. F. Cordeiro, “Neuroprotection in glaucoma: is there a future role?” Experimental Eye Research, vol. 91, no. 5, pp. 554–566, 2010.

R. Naskar, M. Wissing, and S. Thanos, “Detection of early neuron degeneration and accompanying microglial responses in the retina of a rat model of glaucoma,” Investigative Ophthalmology and Visual Science, vol. 43, no. 9, pp. 2962–2968, 2002.

R. M. Sappington, M. Chan, and D. J. Calkins, “Interleukin-6 promotes retinal ganglion cells from pressure-induced death,” Investigative Ophthalmology and Visual Science, vol. 47, no. 7, pp. 2932–2942, 2006.

G. Tezel, “TNF-α signaling in glaucomatous neurodegeneration,” Progress in Brain Research, vol. 173, pp. 409–421, 2008.

X. Zhou, F. Li, L. Kong, H. Tomita, C. Li, and W. Cao, “Involvement of inflammation, degradation, and apoptosis in a mouse model of glaucoma,” The Journal of Biological Chemistry, vol. 280, no. 35, pp. 31240–31248, 2005.

A. Bosco, M. R. Steele, and M. L. Vetter, “Early microglia activation in a mouse model of chronic glaucoma,” Journal of Comparative Neurology, vol. 519, no. 4, pp. 599–620, 2011.

S. Taylor, C. J. Calder, J. Albion, J. T. Erischen, M. E. Boulton, and J. E. Morgan, “Involvement of the CD200 receptor complex in microglia activation in experimental glaucoma,” Experimental Eye Research, vol. 92, no. 5, pp. 338–343, 2011.

R. de Hoz, B. I. Gallego, A. I. Ramirez et al., “Rod-like microglia are restricted to eyes with laser-induced ocular hypertension but absent from the microglial changes in the contralateral untreated eye,” PLoS ONE, vol. 8, no. 12, Article ID e83733, 2013.

T. M. Tikka and J. E. Keistinaho, “Minocycline provides neuroprotection against N-methyl-D-aspartate neurotoxicity by inhibiting microglia,” Journal of Immunology, vol. 166, no. 12, pp. 7527–7533, 2001.

A. Bosco, D. M. Inman, M. R. Steele et al., “Reduced retina microglial activation and improved optic nerve integrity with minocycline treatment in the DBA/2J mouse model of glaucoma,” Investigative Ophthalmology and Visual Science, vol. 49, no. 4, pp. 1437–1446, 2008.

D. S. Fong, L. P. Aiello, F. L. Ferris III, and R. Klein, “Diabetic retinopathy,” Diabetes Care, vol. 27, no. 10, pp. 2540–2553, 2004.

A. R. Santiago, A. J. Cristóvão, P. F. Santos, C. M. Carvalho, and A. F. Ambrósio, “High glucose induces caspase-independent cell death in retinal neural cells,” Neurobiology of Disease, vol. 25, no. 3, pp. 464–472, 2007.

A. J. Barber, “A new view of diabetic retinopathy: a neurodegenerative disease of the eye,” Progress in NeuroPsychopharmacology and Biological Psychiatry, vol. 27, no. 2, pp. 283–290, 2003.

A. J. Barber, E. Lieth, S. A. Khin, D. A. Antonetti, A. G. Buchanan, and T. W. Gardner, “Neural apoptosis in the retina during experimental and human diabetes: early onset and effect of insulin,” Journal of Clinical Investigation, vol. 102, no. 4, pp. 783–791, 1998.

A. M. A. El Asrar, D. Mainone, P. H. Morse, S. Gregory, and A. T. Reder, “Cytokines in the vitreous of patients with proliferative diabetic retinopathy,” American Journal of Ophthalmology, vol. 114, no. 6, pp. 731–736, 1992.

T. Yuuki, T. Kanda, Y. Kimura et al., “Inflammatory cytokines in vitreous fluid and serum of patients with diabetic vitreoretinopathy,” Journal of Diabetes and Its Complications, vol. 15, no. 5, pp. 257–259, 2001.

J. J. Patel, G. M. Saleh, P. G. Hykin, Z. J. Gregor, and I. A. Cree, “Concentration of haemodynamic and inflammatory related cytokines in diabetic retinopathy,” Eye, vol. 22, no. 2, pp. 223–228, 2008.

M. T. Schram, N. Chaturvedi, C. G. Schalkwijk, J. H. Fuller, and C. D. A. Stehouwer, “Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes—the EURODIAB Prospective Complications Study,” Diabetologia, vol. 48, no. 2, pp. 370–378, 2005.

N. Demircan, B. G. Safran, M. Soylu, A. A. Ozcan, and S. Sizmaz, “Determination of vitreous interleukin-1 (IL-1) and tumour necrosis factor (TNF) levels in proliferative diabetic retinopathy,” Eye, vol. 20, no. 12, pp. 1366–1369, 2006.

C. Gustavsson, E. Agardh, B. Bengtsson, and C. D. Agardh, “TNF-α is an independent serum marker for proliferative retinopathy in type 1 diabetic patients,” Journal of Diabetes and Its Complications, vol. 22, no. 5, pp. 309–316, 2008.

A. Carmo, J. G. Cunha-Vaz, A. P. Carvalho, and M. C. Lopes, “L-arginine transport in retinas from streptozotocin diabetic rats: Correlation with the level of IL-1β and NO synthase activity,” Vision Research, vol. 39, no. 23, pp. 3817–3823, 1999.

R. A. Kowluru and S. Odenbach, “Role of interleukin-1β in the pathogenesis of diabetic retinopathy,” British Journal of Ophthalmology, vol. 88, no. 10, pp. 1343–1347, 2004.

C. Gerhardinger, M. B. Costa, M. C. Coulombe, I. Toth, T. Hoehn, and P. Grosu, “Expression of acute-phase response proteins in retinal Müller cells in diabetes,” Investigative Ophthalmology and Visual Science, vol. 46, no. 1, pp. 349–357, 2005.

J. K. Krady, A. Basu, C. M. Allen et al., “Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy,” Diabetes, vol. 54, no. 5, pp. 1559–1565, 2005.

A. M. Joussen, V. Poulaki, N. Mitsiades et al., “Nonsteroidal anti-inflammatory drugs prevent early diabetic retinopathy via TNF-alpha suppression,” The FASEB Journal, vol. 16, no. 3, pp. 438–440, 2002.

Y. Behl, P. Krothapalli, T. Desta, A. DiPiazza, S. Roy, and D. T. Graves, “Diabetes-enhanced tumor necrosis factor-α production promotes apoptosis and the loss of retinal microvascular cells in type 1 and type 2 models of diabetic retinopathy,” The American Journal of Pathology, vol. 172, no. 5, pp. 1411–1418, 2008.

C. Gustavsson, E. Agardh, B. Bengtsson, and C. D. Agardh, “TNF-α is an independent serum marker for proliferative retinopathy in type 1 diabetic patients,” Journal of Diabetes and Its Complications, vol. 44, no. 5, pp. 2184–2191, 2003.

E. C. Leal, A. Manivannan, K. Hosoya et al., “Inducible nitric oxide synthase isoform is a key mediator of leukostasis and blood-retinal barrier breakdown in diabetic retinopathy,” Investigative Ophthalmology and Visual Science, vol. 48, no. 11, pp. 5257–5265, 2007.

C. A. Aveleira, C. M. Lin, S. F. Abcouwer, A. F. Ambrósio, and D. A. Antonetti, “TNF-α signals through PKCζ/NF-κB to alter the tight junction complex and increase retinal endothelial cell permeability,” Diabetes, vol. 59, no. 11, pp. 2872–2882, 2010.

G. N. Costa, J. Vindeirinho, C. Cavadas, A. F. Ambrósio, and P. F. Santos, “Contribution of TNF receptor 1 to retinal neural cell death induced by elevated glucose,” Molecular and Cellular Neuroscience, vol. 50, no. 1, pp. 113–123, 2012.
H. Zeng, W. R. Green, and M. O. M. Tso, “Microglial activation in human diabetic retinopathy,” Archives of Ophthalmology, vol. 126, no. 2, pp. 227–232, 2008.

A. J. Barber, D. A. Antonetti, T. S. Kern et al., “The Ins2Akita mouse as a model of early retinal complications in diabetes,” Investigative Ophthalmology and Visual Science, vol. 46, no. 6, pp. 2210–2218, 2005.

A. S. Ibrahim, A. B. El-Remessy, S. Matragoon et al., “Retinal microglial activation and inflammation induced by amadori-glycated albumin in a rat model of diabetes,” Diabetes, vol. 60, no. 4, pp. 1122–1133, 2011.

X. X. Zeng, Y. K. Ng, and E. A. Ling, “Neuronal and microglial response in the retina of streptozotocin-induced diabetic rats,” Visual Neuroscience, vol. 17, no. 3, pp. 463–471, 2000.

S. Omri, F. Behar-Cohen, Y. de Kozak et al., “Microglia/macrophages migrate through retinal epithelium barrier by a transcellular route in diabetic retinopathy: role of PKCζ in the Goto Kakizaki rat model,” The American Journal of Pathology, vol. 179, no. 2, pp. 942–953, 2011.

N. N. Osborne, R. J. Casson, J. P. M. Wood, G. Chidlow, M. Graham, and J. Melena, “Retinal ischemia: mechanisms of damage and potential therapeutic strategies,” Progress in Retinal and Eye Research, vol. 23, no. 1, pp. 91–147, 2004.

T. T. Lam, A. S. Abler, and M. O. M. Tso, “Apoptosis and caspases after ischemia-reperfusion injury in rat retina,” Investigative Ophthalmology and Visual Science, vol. 40, no. 5, pp. 967–975, 1999.

H. A. Quigley, “Neuronal death in glaucoma,” Progress in Retinal and Eye Research, vol. 18, no. 1, pp. 39–57, 1999.

N. N. Osborne, J. Melena, G. Chidlow, and J. P. M. Wood, “A hypothesis to explain ganglion cell death caused by vascular insults at the optic nerve head: possible implication for the treatment of glaucoma,” The British Journal of Ophthalmology, vol. 85, no. 10, pp. 1252–1259, 2001.

G. J. Ghiardi, J. M. Gidday, and S. Roth, “The purine nucleoside adenosine in retinal ischemia-reperfusion injury,” Vision Research, vol. 39, no. 15, pp. 2519–2535, 1999.

B. Li, P. S. Rosenbaum, N. M. Jennings, K. M. Maxwell, and S. Roth, “Differing roles of adenosine receptor subtypes in retinal ischemia-reperfusion injury in the rat,” Experimental Eye Research, vol. 68, no. 1, pp. 9–17, 1999.

T. Konno, A. Sato, T. Uchibori, A. Nagai, K. Kogi, and N. Nakahata, “Adenosine A2A receptor mediated protective effect of 2-(6-cyano-1-hexyn-1-yl)adenosine on retinal ischaemia/reperfusion damage in rats,” British Journal of Ophthalmology, vol. 90, no. 7, pp. 900–905, 2006.

K. D. Steinsapir and R. A. Goldberg, “Traumatic optic neuropathy,” Survey of Ophthalmology, vol. 38, no. 6, pp. 487–518, 1994.

S. Ahmad, N. Fattah, N. M. El-Sherbiny et al., “Potential role of A2A adenosine receptor in traumatic optic neuropathy,” Journal of Neuroimmunology, vol. 264, no. 1-2, pp. 54–64, 2013.

E. Garcia-Valenzuela and S. C. Sharma, “Laminar restriction of retinal macrophagic response to optic nerve axotomy in the rat,” Journal of Neurobiology, vol. 40, no. 1, pp. 55–66, 1999.

C. Zhang and M. O. M. Tso, “Characterization of activated retinal microglia following optic axotomy,” Journal of Neuroscience Research, vol. 73, no. 6, pp. 840–845, 2003.

S. G. Wohl, C. W. Schmeer, O. W. Witte, and S. Isenmann, “Proliferative response of microglia and macrophages in the adult mouse eye after optic nerve lesion,” Investigative Ophthalmology and Visual Science, vol. 51, no. 5, pp. 2686–2696, 2010.

J. Vindeirinho, G. N. Costa, M. B. Correia, C. Cavadas, and P. F. Santos, “Effect of diabetes/hyperglycemia on the rat retinal adenosinergic system,” PLoS ONE, vol. 8, no. 6, Article ID e67499, 2013.

N. M. Elsherbiny, S. Ahmad, M. Naima et al., “ABT-702, an adenosine kinase inhibitor, attenuates inflammation in diabetic retinopathy,” Life Sciences, vol. 93, no. 2-3, pp. 78–88, 2013.

M. Madeira, F. Elvis, J. Martins, A. F. Ambrósio, and A. R. Santiago, “adenosine A2AR blockade prevents retinal microglial activation,” in Proceedings of the 22nd IUBMB 37th FEBS Congress, Blackwell, Seville, Spain, 2012.