ImmunoTools IT-Box-Cy55M-Award 2013

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Controlling neuroinflammation in the retina through A2AR modulation: potential therapeutic implication in glaucoma

Glaucoma is characterized by loss of retinal ganglion cells (RGCs) and optic nerve damage, accompanied by an inflammatory response involving microglia and RGCs.

Blockade of adenosine A2A receptor (A2AR) has been suggested to confer robust neuroprotection in several neurodegenerative conditions involving neuroinflammation (Cunha, 2005; Rebola, 2011) It is still unknown the role of A2AR in RGC neuroprotection in glaucoma. Our preliminary results demonstraed that blockade of A2AR can inhibit retinal microglial cell reactivity. We hypothesize that A2AR blockade controls retinal neuroinflammation, thus protecting RGCs in glaucoma models.

The main aims of the project is to investigate whether the modulation of A2AR activity controls retinal microglia-induced neuroinflammation.

Although the role of inflammatory cytokines in glaucoma is not been yet completely clarified, several cytokines have been identified as main players in the development of this disease. Increased production of TNF-α as been related with the death of RGCs in models of glaucoma (Tezel, 2000). Also, it has been demonstrated that IL-6 protects RGCs from pressure-induced death (Sappington, 2006). In addition, it was previously described that inflammatory cytokines can regulate function and expression of A2AR (Khoa, 2001). Therefore, we also will also investigate the role of pro- and anti-inflammatory cytokines in the modulation of A2AR and on retinal microglial reactivity.

The ImmunoTools *T-Box-Cy55M* contains GM-CSF, which will be required for maintanence and culture of purified retinal microglial cells. Microglial cells will be stimulated with LPS plus interferon gamma, incubated with several cytokines, (rm IL-10, rm IL-1beta, and rm IL-6), and exposed to elevated hydrostatic pressure (to mimic elevated intraocular pressure, the main risk factor of glaucoma). We aim to investigate the role played by A2AR in the control of microglial cell reactivity, and which cytokines control A2AR expression.

This work will contribute to a better understanding of the neuroinflammatory process that occurs in models of glaucoma. With this information we can possibly suggest pathways that can be modulated in order to decrease the exarbated inflammatory response, characteristic of a neurodegenerative disease.

References:

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