Intravitreal Injection of Resolvin D1 Counteracts the Ocular Damage Induced by Systemic LPS in a Murine Model of Endotoxic Uveitis

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The mainstay of human uveitis treatment tends to inhibit the immune response by systemic agents10 and, more recently, anti–interleukin (IL)-2 receptor antibody 2 (Nussenblatt et al., 1999), anti-alpha interferon (Kotter et al., 2003) or drugs inhibiting the binding of tumor necrosis factor alpha (TNF)-α to its receptors (Mendelsohn et al., 1998). These strategies are successfully used in patients with recalcitrant uveitis; however, because of their systemic administration, all these drugs induce potentially severe adverse effects. Moreover, in certain ocular tissues, tight junctions reduce the passage of drugs from the blood to the eye, thus limiting the bioavailability of immunosuppressors in ocular tissues.

To overcome these limitations, local administration of drugs directly into the eye is particularly interesting for treating ocular diseases. We tested here the possibility to administrate the novel pro-resolution promoter Resolvin D1 directly into the vitreous, in order to promote local resolution of the inflammation and repair of the injured tissue induced by uveitis.

24 h after the administration of 200 μg LPS into the footpad of Sprague-Dawley rats severe changes of the structure of the eye. These were scored ~4 as for the following score: 0= no inflammatory reaction; 1= discrete dilation of iris and conjunctival vessels; 2 =moderate dilation of iris and conjunctival vessels with moderate flare in the anterior chamber; 3 = intense iridal hyperemia with intense flare in the anterior chamber; 4 = same clinical signs as 3 with presence of fibrinoid exudation in the pupillary area and miosis. In rats with LPS induced uveitis ocular tissue showed an increase of ubiquitin-proteasome system associated with enhanced NFKB and TNF-α.

Intravitreal Resolvin D1 (RvD1; 10-100-1000 ng/kg in 4 μl of sterile saline) injection dose-dependently prevents the development of the ocular inflammation caused by LPS, and improved the clinical score attributed to EIU in a dose-dependent manner. RvD1 causes a strong reduction of T-lymphocytes $CD4^+$, $CD8^+$ and B-lymphocytes $CD20^+$ within the eye affected by LPS induced uveitis. RvD1 also reduced the UPS and NFKB expression and cytokines TNF-alpha., reducing severe inflammatory and immune response occurring within the eye.

In conclusion, our study demonstrated that intravitreal Resolvin D1 injection in rats, undergoing experimental uveitis, reduced the eye immuno-inflammatory reaction, accounting for eye protection. Particularly, we hypothesize ubiquitin-proteasome system overactivity is associated with enhanced immuno-inflammatory reaction in rats treated with LPS. The inhibition of ubiquitin-proteasome in rats by intravitreal RVD1 injction is associated with decrease of immuno-inflammatory eye reaction, possibly by downregulating NFkB-mediated inflammatory pathways.

Nussenblatt et al. (1999) *Proc Natl Acad Sci USA*. 96, 7462–7466
Kotter et al., *(2003) Adv Exp Med Biol*. 528, 521–523
Mendelsohn et al., (1998) *Arch Ophthalmol*. 116, 1209–1212