PRINCIPE FELIPE
CENTRO DE INVESTIGACION

CIPF Seminar

Pharmacologic therapies to treat inherited retinal dystrophies

Speaker: **Regina Rodrigo**
IIS La Fe
Date: **07/05/19- 12:30h**
Place: Salón de Actos CIPF

Retinitis Pigmentosa (RP) is the most common form of inherited retinal dystrophy. Although RP is considered a rare disease this is one of the most common forms of inherited retinal degeneration, constituting the largest single cause of inherited blindness in the developed world. RP is highly heterogeneous, genetically and clinically. It is characterized by progressive rod-dominant photoreceptor degeneration in the initial stage of the disease and follows with cone degeneration in later stages. It is probable that cone degeneration is influenced by the release of oxidant radicals, inflammatory molecules, etc. from rods and other cells, independently of gene mutation. Despite the fact that many technically diverse approaches are being investigated for the treatment of RP, there is currently no standardized and efficient treatment.

We observed that oxidative stress and inflammatory processes, including upregulation of the pleiotropic cytokine TNFα are closely linked to retinal degeneration in rd10 mice, a murine model of RP. This also happens in ex vivo models of human or porcine retinal explants exposed to Zaprinast1,2, which induces retinal degeneration. Besides, we found upregulation of cytokines and oxidative stress in aqueous humor and blood from RP patients3. Binding of TNFα to TNFα receptors triggers several well-characterized death-promoting events. We found evidence that antibodies against TNFα including Infliximab and Adalimumab ameliorate retinal degeneration in rd10 mice and porcine retinas exposed to zaprinast2,4. On the other hand, inappropriate oxygen supply and consumption could also contribute to the pathogenesis of RP. It has been shown that rods consume most of the oxygen in the retina and their death could increase oxygen concentration, which in turns reduce hypoxia-inducible factor 1 (HIF-1α) and contribute to cone cell death. In this regard, we demonstrated a generalized downregulation of HIF-1α suggesting the presence of high oxygen levels during retinal degeneration in rd10 mice. Elevated oxygen can be responsible for oxidative stress and reduced antioxidant response found in RP patients and rd10 mice. In agreement with this finding, we demonstrated that the use of a prolyl hydroxylase inhibitor, DMOG, diminished photoreceptor cell death in rd10 mice5.

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2. Martínez-Fernández de la Cámara C, Hernández-Pinto A, Olivares-González L, Cuevas-Martín C, Sánchez-Aragó M, Hervás D, Salom D, Cuezva JM, de la Rosa EJ, Millán JM, Rodrigo R. Adalimumab reduces photoreceptor cell death in a mouse model of retinal degeneration. Sci ReportsSci. Rep. (2015) 5, 11764; doi: 10.1038/srep11764
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5. Olivares-González, Martínez-Fernández de la Cámara C, Hervás D, Millán JM, Rodrigo R. HIF-1α stabilization reduces retinal degeneration in mouse model of retinitis pigmentosa. FASEB J. 2018) 32(5):2438-2451.

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