



Proc Natl Acad Sci USA Participation of RXR α in the control of innate immunity identifies it as a possible therapeutic target for the treatment of sepsis



Retinoid X receptor α controls innate inflammatory responses through the up-regulation of chemokine expression

V. Núñez, D. Alameda, D. Rico, R. Mota, P. Gonzalo, M. Cedenilla, T. Fischer, L. Boscá, C. K. Glass, A. G. Arroyo, and M. Ricote
Proc Natl Acad Sci U S A. 2010 Jun 8;107(23):10626-31

[Link al artículo](#)

The innate immune system is the most ancient form of organismal defense against foreign substances such as microorganisms, with inflammation being one of the first responses of this system to infection. Normally the organism is able to control this inflammation; however, infection by certain microorganisms can provoke uncontrolled inflammation, resulting in the death of the organism in a process known as sepsis. Today, sepsis is the primary cause of death among patients in intensive care units, and its incidence has increased significantly in recent years, accounting for 12000 deaths a year in Spain.

Nuclear receptors are a group of transcription factors that when activated by specific ligands regulate the expression of numerous genes. These receptors regulate several aspects of growth, development and homeostasis, and also play an important role in diseases such as diabetes, atherosclerosis and cancer. Although several members of the nuclear receptor family have emerged recently as important regulators of the immune response, the existence of a signaling pathway in macrophages mediated by retinoid X receptor (RXR) had not been explored. RXR is a key member of the nuclear receptor family because several other nuclear receptors must dimerize with RXR in order to regulate the transcription of their target genes. RXR function requires activation by ligands derived from vitamin A, such as 9 cis-retinoic acid. Some RXR ligands are in current use for the treatment of certain types of cancer.

The study, carried out at the CNIC by Vanessa Nuñez and Daniel Alameda in the laboratory of [Dr. Mercedes Ricote](#), demonstrates that RXR regulates the expression of two chemokine mediators of inflammation, CCL6 and CCL9, which play important roles in the migration of macrophages. The chemokines were identified in a microarray screen for genes regulated by RXR in macrophages. To explore the mechanism by which RXR regulates these chemokines, the team conducted a range of molecular biological analyses, which showed that the regulation of CCL6 and CCL9 is specific to RXR and independent of other nuclear receptors. These results suggest that RXR is an important inflammatory mediator in macrophages during the innate immune response.

Although the existence of a signaling pathway independent of other nuclear receptors has been described in other studies, its demonstration in vivo has remained a challenge in the field. To tackle this question, the group at the CNIC generated genetically modified mice that lack the gene for RXR α specifically in macrophages. Studies of these mice in different models of peritonitis showed that they are defective in the recruitment of leukocytes to sites of inflammation and also survive sepsis for longer than normal mice. This part of the study was conducted together with the group of [Dr. Alicia G. Arroyo](#), also of the CNIC, and the study also involved collaborations with other national and international groups.

The results of this study, published in the Proceedings of the National Academy of Science, demonstrate that the nuclear receptor RXR is a potential therapeutic target for the treatment and prevention of sepsis as well as chronic inflammatory diseases such as diabetes and atherosclerosis.

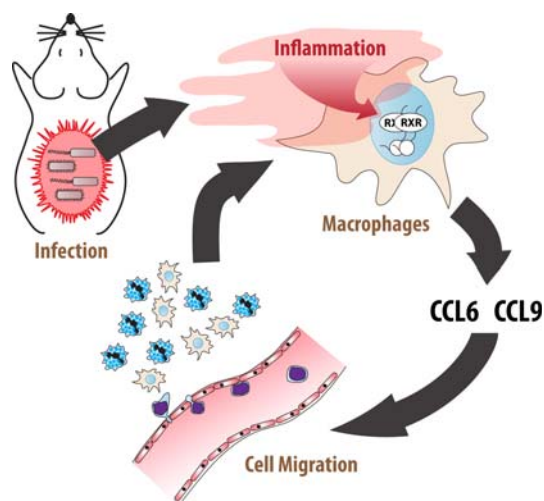


Figure: Summary scheme of the PNAS article