Role of Lipid Mediators in Hepatic Steatosis, Inflammation and Fibrosis

Dr. Joan Clària
Department of Biochemistry and Molecular Genetics
Hospital Clínic
University of Barcelona

There is growing recognition of the importance of inflammation in initiating the sequence of events leading to liver injury. Following an insult of any etiology, the liver develops a localized inflammatory response, which serves to destroy, dilute or wall off the injurious agent and the injured tissue. If the insult persists or the inflammatory response remains uncontrolled or is not properly resolved, this response becomes chronic and ultimately leads to the formation of tissue scar, fibrosis and eventually cirrhosis. Among the different mediators involved in inflammation and liver injury, those derived from the omega-6-polyunsaturated fatty acid arachidonic acid are the best characterized. This family of pro-inflammatory lipid mediators include classical eicosanoids such as prostaglandins and leukotrienes, as well as other more recently described molecules. On the other hand, a novel family of lipid mediators derived from the omega-3 fatty acids docosahexanoic and eicosapentaenoic acids has been recently identified and characterized. These lipid mediators are designated resolvins, protectins and maresins, carry potent anti-inflammatory and pro-resolving properties, work as endogenous “stop signals” and promote the resolution of inflammation. This seminar will review the most relevant findings on the role of bioactive lipid mediators in the pathogenesis of hepatic inflammation and fibrosis and will also uncover novel functions of these mediators in the regulation of hepatic steatosis. The seminar will also provide new views on the role of endogenously-generated omega-3 fatty acid-derived lipid mediators in nonalcoholic fatty liver disease (NAFLD) and in controlling obesity-related unremitting inflammation in the visceral adipose tissue, which has a direct impact on insulin-sensitive tissues such as the liver.

CURRICULUM VITAE

Joan Clària is currently a Senior Consultant at the *Clinical Laboratory Service: Biochemistry and Molecular Genetics* of the *Hospital Clínic of Barcelona*. He is also an Associate Professor at the *Department of Physiological Sciences I* at the *School of Medicine* of the *University of Barcelona*. He was trained as a specialist in Clinical Biochemistry and initiated his scientific career as a research fellow from 1987 to 1992 at the *Liver Unit* of the *Hospital Clínic of Barcelona*. From 1993 to 1996 he performed his post-doctoral studies as a Fulbright scholar at the *Brigham and Women's Hospital and Harvard Medical School* (Boston, MA) with Professor Charles N. Serhan, a leading scientist in the resolution of inflammation. He has also been a Visiting Scientist at the *University of North Carolina* (Chapel Hill, NC) (2001) and *The Jackson Laboratory* (Bar Harbor, ME) (2007) and a Visiting Professor at the *Harvard Institutes of Medicine* (*Brigham and Women's Hospital/Harvard Medical School*) (Boston, MA) (2010-2011). His laboratory is mainly interested in

the study of lipid mediators implicated in the resolution of inflammation, with a special emphasis on the role of specialized pro-resolving mediators derived from omega-3-PUFA in obesity-associated liver complications. He is a member of the Editorial Boards of Gut, Lipids Insight, World Journal of Immunology, Frontiers in Lipidology and Metabolism, World Journal of Hepatology and World Journal of Gastrointestinal Pharmacology and Therapeutics. He is the current President of the European Society for Lipid Mediators.

Relevant publications for the last 5 years:

López-Vicario C, Alcaraz-Quiles J, García-Alonso V, Rius B, Hwang SE, Titos E, Lopategi A, Hammock B, Arroyo V, Clària J. Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver. Role for omega-3 epoxides. **Proc Natl Acad Sci U S A** 2014 Dec 30. pii: 201422590.

Rius B, Titos E, Morán-Salvador E, López-Vicario C, García-Alonso V, González-Périz A, Arroyo V, Clària J. Resolvin D1 primes the resolution process initiated by calorie restriction in obesity-induced steatohepatitis. **FASEB J** 2014;28:836-48

López-Vicario C, González-Périz A, Rius B, Morán-Salvador E, García-Alonso V, Lozano JJ, Bataller R, Cofán M, Kang JX, Arroyo V, Clària J, Titos E. A regulatory loop between desaturases and omega-3 fatty acids exerts protective actions in obesity-induced fatty liver disease. **Gut** 2014;63:344-55

Spite M, Clària J and Serhan C.N. Resolvins, Specialized Pro-Resolving Lipid Mediators and their Potential Roles in Metabolic Syndrome. **Cell Metab.** 2014;19:21-36

Morán-Salvador E, Titos E, González-Périz A, Rius B, García-Alonso V, López-Vicario C, Miquel R, Barak Y, Arroyo V, Clària J. Cell-specific knockout mice establish anti-inflammatory and anti-fibrogenic properties for PPARγ in non-parenchymal liver cells. **J Hepatol** 2013;59:1045-1053

García-Alonso V, López-Vicario C, Titos E, Morán-Salvador E, González-Périz A, Rius B, Parrizas M, Werz O, Arroyo V, Clària J. Coordinate functional regulation between microsomal prostaglandin E synthase-1 and PPARγ in the conversion of white-to-brown adipocytes. **J Biol Chem** 2013;288;28230-28242

Clària J, Dalli J, Yacoubian S, Gao F, Serhan CN. Resolvin D1 and Resolvin D2 Govern Local Inflammatory Tone in Obese Fat. **J Immunol** 2012;189:2597-2605

Titos E, González-Périz A, López-Vicario C, Rius B, Morán- Salvador E, Martínez-Clemente M, Arroyo V, Clària J. Resolvin D1 and its Precursor Docosahexaenoic Acid Promote Resolution of Adipose Tissue Inflammation by Eliciting Macrophage Polarization toward a Pro-Resolving Phenotype. **J Immunol** 2011;187:5408-18

Morán-Salvador, López-Parra M, García-Alonso V, Titos E, Martínez-Clemente M, González-Périz A, López-Vicario C, Barak Y, Arroyo V, Clària J. Role for PPARγ in obesity-induced hepatic steatosis as determined by hepatocyte and macrophage-specific conditional knockouts. **FASEB J** 2011;25:2538-50

Martínez-Clemente M, Ferré N, Titos E, Horrillo R, González-Périz A, Morán-Salvador E, López-Vicario C, Miquel R, Arroyo V, D Funk C, Clària J. Disruption of the 12/15-lipoxygenase gene (Alox15) protects hyperlipidemic mice from nonalcoholic fatty liver disease. **Hepatology** 2010;52:1980-1991

Martínez-Clemente M, Ferré N, González-Périz A, López-Parra M, Horrillo R, Titos E, Morán-Salvador E, Planagumà A, Miquel R, Arroyo V, Funk CD, Clària J. 5-Lipoxygenase Deficiency Reduces Hepatic Inflammation and TNFalpha-induced Hepatocyte Damage in Hyperlipidemia-prone ApoE-null Mice. **Hepatology** 2010;51:817-827.