

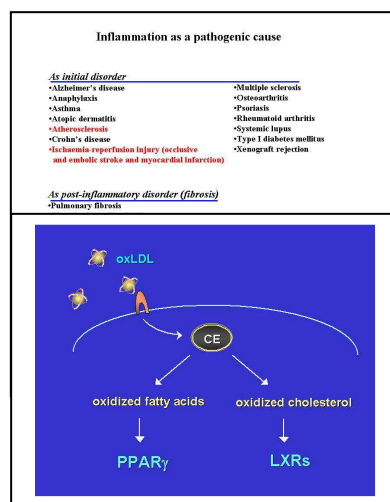
Inflammation, Nuclear Receptors and Atherogenesis

BOSCA, Lisardo

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CSIC-CNIC. Centro Nacional de Investigaciones Cardiovasculares Melchor Fernández Almagro 3, 28029 Madrid

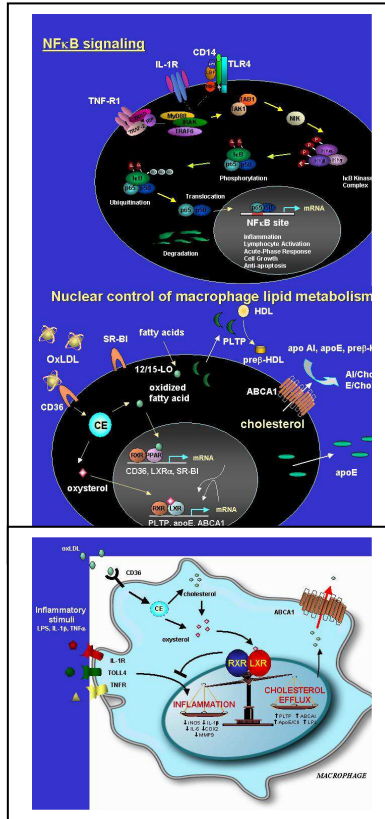
Recent advances in the establishment of the molecular basis of the pathogenesis has been possible after the consideration of the inflammatory reaction as a relevant cause in the development of diseases as different as cancer, neurodegeneration and cardiovascular pathology, among other. In all these cases inflammation has been considered as an original cause of pathogenesis, but also as a consequence in an attempt of the tissue to resolve an inflammatory process as occurs in most cases of fibrosis in the lung, liver and to some extent in the vascular system. In this sense, the identification of the molecular basis of the inflammatory response as well as those pathways that participate in the resolution of inflammation in the cardiovascular system has allowed to open new points of view on the physiopathology of atherosclerosis, and therefore, on the treatment of the cardiovascular diseases.



The oxidation of the LDL and/or the occurrence of systemic infectious processes are behind the recruitment of monocytes and other inflammatory cells to the intima and the final differentiation of activated macrophages to foam cells, a situation that is responsible, at least in part for the process of the development of the atherome lesion. Indeed, the impairment of the mechanisms associated to the negative control of the inflammatory response and the resolution of inflammation has been demonstrated to occur in many cases (if not in all non-genetically determined vascular dysfunction). In this regard, it has been described failure in the mechanisms that governs the negative regulation of the transcriptional activity depending on the activation of

transcription factors such as NF- κ B, Stat-1 or IRF-1, and to a lower extend those depending on AP-1 activation, therefore exhibiting an enhanced transcription of genes involved in inflammation. Recent studies from various groups has revealed that an efficient resolution of inflammation in the vascular system depends on the sequential expression and activation of nuclear receptors of the PPAR γ and LXR α family, both acting as heterodimers with RXR receptors. PPAR γ is normally absent in circulating monocytes but its expression is upregulated as result of the transvasation and differentiation to macrophages. Upon activation by metabolites of arachidonic acid, as well as oxidized fatty acids, PPAR γ governs the expression of a reduced set of genes, among them LXR α and scavenger receptors (CD36 and SR-BI). Since LXRs are activated by cholesteryl esters (oxyesterols), the expression of genes involved in activation of fatty acid metabolism (fatty acid synthase, PLTP, CTPs) and in the efflux of cholesterol (ABCA1) from the macrophage, their function is critical to avoid the accumulation of cholesterol droplets and the terminal differentiation to foam cells. Under dual activation of PPAR and LXR by their physiological activators the expression of inflammatory genes is repressed and the enhancement of lipid disposal is improved. This dual action accomplished through the activation of nuclear receptors is critical in preventing necrotic death in the intima and the deposition of collagens and other extracellular matrix proteins characteristics of the atherome plaque. Indeed, the improvement of the reverse transport of

cholesterol via the overexpression of transporters of the ABC cassette family, in particular ABCA1 as well as scavenger receptors is critical for the efficiency in the macrophage function.



The characterization of the anti-inflammatory and anti-atheromatous mechanisms identified in rodent models needs an extrapolation to primate and human since the genes involved, although notably conserved, exhibit marked biological differences in terms of the structure of the genes, the existence of splicing variants in the case of human, and the presence of polymorphic regions in these genes whose biological relevance, either as markers with prediction value or with functional alterations of the transcriptional/transrepressor activity needs to be evaluated in the future. Finally, the availability of drugs that are pharmacological activators of PPARs and LXRs open new strategies for the treatment of the atherosclerotic disease. In the presentation I will provide data that support the view that the transrepressing activity of the nuclear receptors, in particular PPAR and LXR, deserves further work to understand the fine tuning between inflammation and lipid disposal in the vascular tissue.