Role of interferon-alpha in the activation of tubular epithelial cell in lupus nephritis (LN)

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Background: Plasmacytoid dendritic cells (pDCs) play a key role in the activation of the autoimmune response in LN. These cells, that infiltrate the kidney of patients with LN at tubulointerstitial level (1,2), are the main producers of INF-alpha whose effects on the renal tubule are poorly understood.

Aim: The aim of the study was to investigate the effects of INF-alpha in renal epithelial cells (RPTEC).

Methods:. Through microarray studies (Illumina), we compared the gene expression profile of RPTEC, stimulated with INF-alpha 100U/ml for 48h, to control cells. We validated microarray results through real time PCR (RT-PCR) and citometry experiments on RPTEC, stimulated with INF-alpha, and through immunohistochemical (IHC) analysis and confocal microscopy on renal biopsies with LN.

Results:

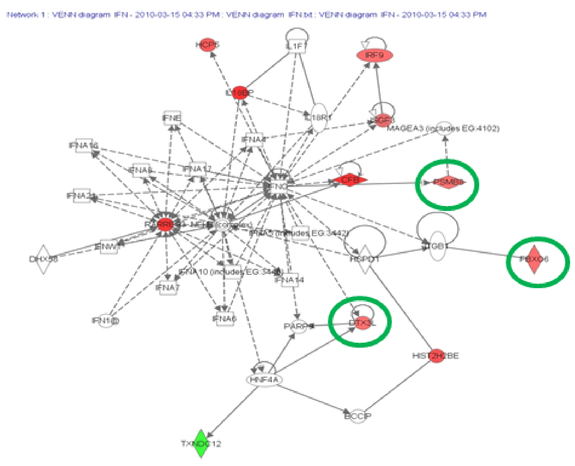

Fig1: The genes that resulted significantly modulated from microarray analyses were studied using Ingenuity™ software. Among the genes up-regulated there were HLA-I, the ubiquitin (FBXO6, DTX3L) and the immunoproteasome subunits LMP7(PSMB8) that were involved in antigen presentation and the inflammatory pathways.

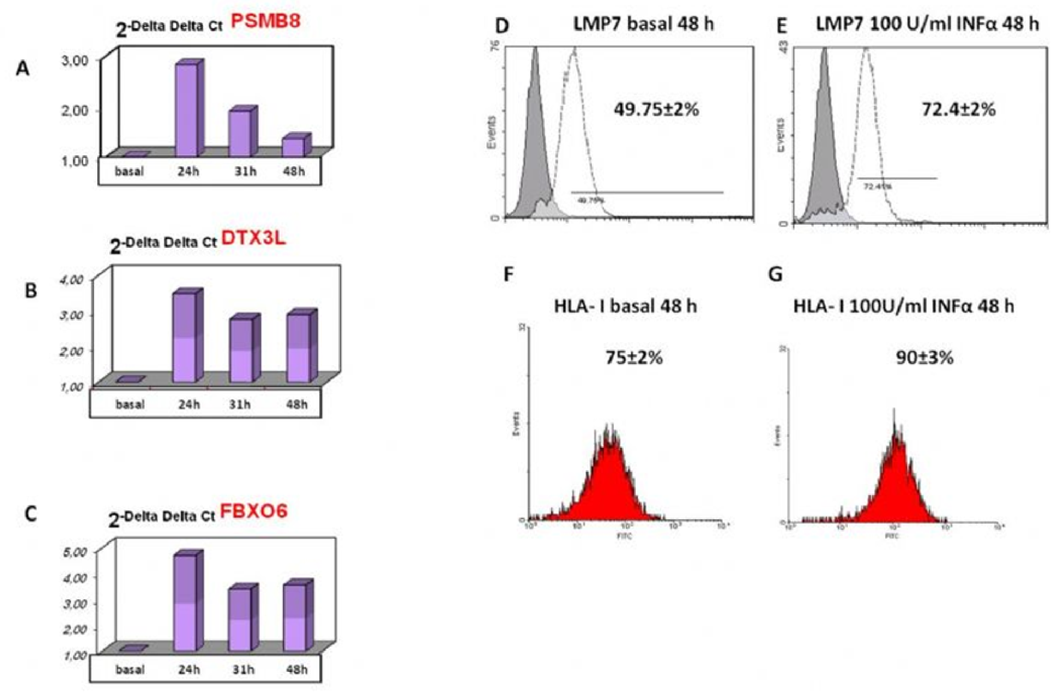

Fig 2: RT-PCR of the ubiquitine (DTXL; FBOX6) and LMP7 subunit on INF-α activated RPTEC **(A, B,C).** Flow citometry on INF-alpha stimulated RPTEC confirmed a significant increase of antigen presentation molecules **(D, E)** and inflammatory signalling **(F, G).**

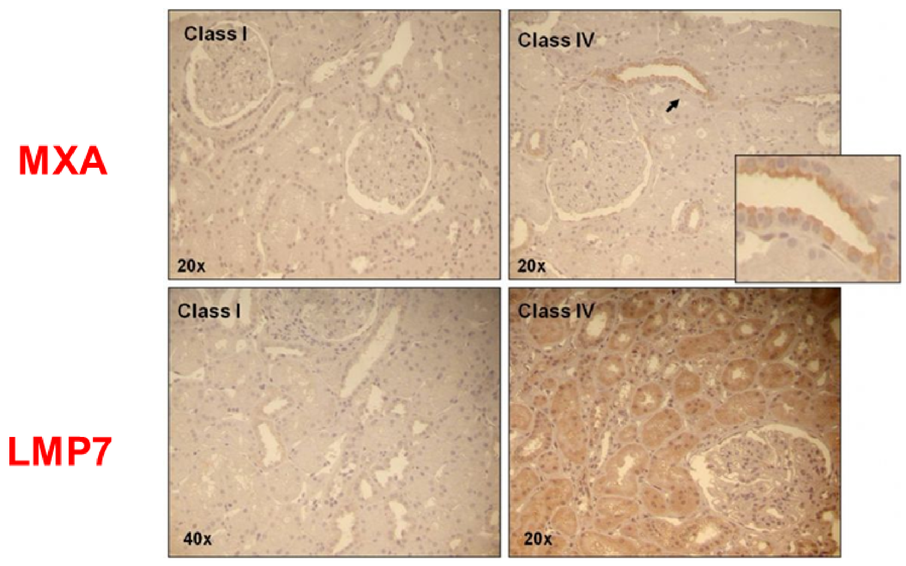

Fig3: IHC analysis on renal biopsies of class IV LN patients showed a significant increase of tubular LMP7 and MXA (marker of INF-alpha local production) expression compared to class I LN.

References:

1.N. Fiore et al Immature myeloid and plasmacytoid dendritic cells infiltrate renal tubule interstitium in patients with lupus nephritis. Molecular Immunology 2008; 45: 259-265

2.G. De Palma et al A role for the chemer23/chemerin axis in the recruitment of dendritic cells in lupus nephritis. Kidney International 2011; 79: 1228-1235

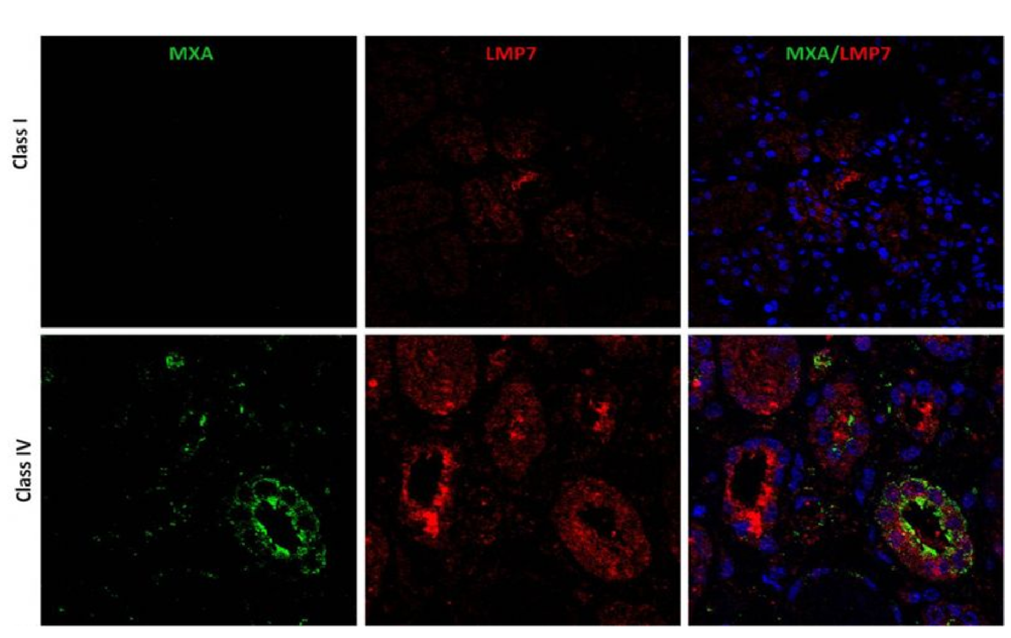

Fig4: Confocal analysis confirmed the colocalization of INF-α signaling with the immunoproteasome (LMP7+/MXA+) in renal tubuli of LN class IV patients.

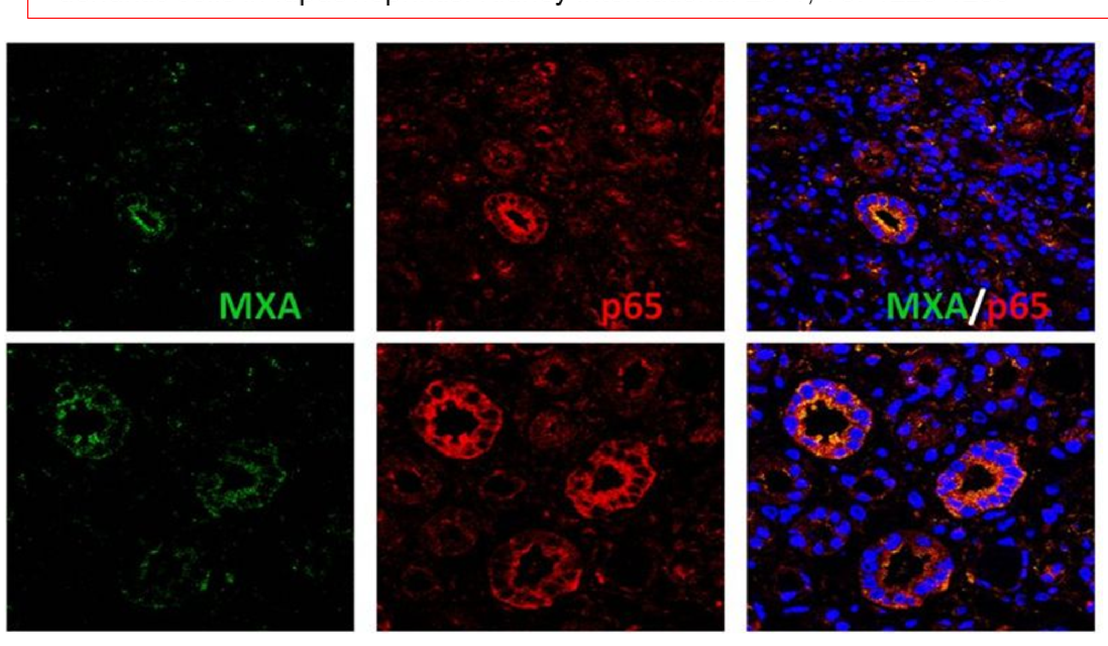

Fig5: Confocal analysis confirmed the activation of inflammatory signalling (NF-KB-p65+/MXA+) in renal tubuli of LN class IV patients

Conclusion: Our data demonstrate that inhibition of INF-alpha pathway could represent a novel therapeutic strategy to reduce renal tubular damage in patients with LN.

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Immune and inflammatory mechanisms

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DOI: 10.3252/pso.eu.50era.2013

Poster presented at: ERA-EDTA 50th Congress Istanbul, Turkey May 15-21, 2013

PosterSessionOnline.com