suPAR and Osteopontin circulating levels in lupus nephritis: an early marker of podocyte damage?

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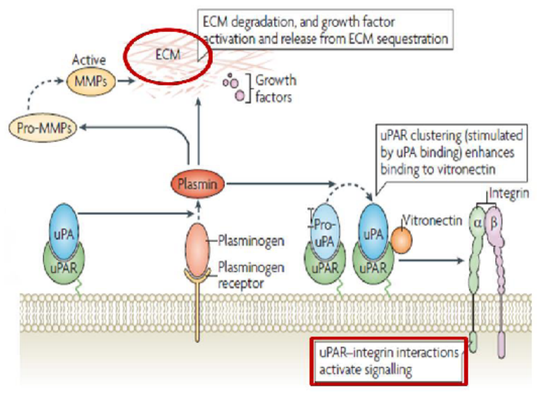
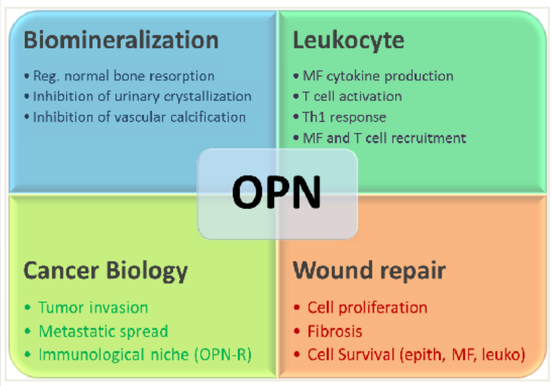
BACKGROUND

High levels of soluble urokinase-type Plasminogen Activator Receptor (suPAR) are associated with nephrotic syndrome and proteinuria in different nephropathies, including minimal change disease, focal segmental glomerulosclerosis and secondary glomerulonephritis.



Osteopontin (OPN) is a pro-inflammatory cytokine which recently has been associated with kidney injury in lupus nephritis. However it is still uncertain if suPAR and OPN induce podocyte damage in vivo or if their increased levels are a consequence of kidney injury.



Aim of this study was to evaluate if and how suPAR and OPN interact in determining podocyte damage in an "in vivo" model of lupus nephritis

METHODS

This study investigates the role of suPAR in inducing podocyte damage in animal models of lupus nephritis (MRL/*lpr* mice). We have taken time-fixed samples for urinary proteins and suPAR circulating levels and monitored for 32 weeks

Moreover we have investigated the relationship between OPN and uPAR/suPAR expression on cultured monocytes and which drugs acting on the renin-angiotensin axis (furosemide, spironolactone, triamterene, valsartan) or heparin (unfractioned) exert a control on suPAR or OPN expression.

Animal model characteristics:

- Strain: MRL-MPJFas^{lpr} (MRL/*lpr*)
- Nephropathy: Immune-complex GN (Lupus nephritis)
- Mesangial proliferation: diffuse, may be severe
- Time of onset: 8-12 weeks
- Other autoAntibodies: ANA, anti ds-DNA, anti GBM

Monocyte culture:

- From healthy donors
- Isolated from PBMC and stimulated with LPS
- Add recombinant OPN (rhOPN) or drugs, for 18h

RESULTS

In the animal model, circulating suPAR level are increased during lupus nephritis and start to rise two weeks before the development of overt proteinuria (Fig. 1).

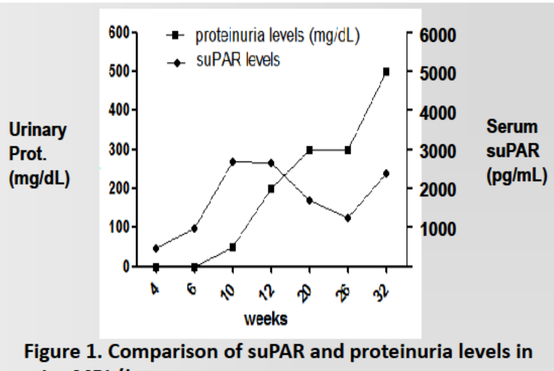


Figure 1. Comparison of suPAR and proteinuria levels in mice MRL/*lpr*

On cultured monocytes, out of the tested drugs only captopril reduced the production of suPAR (Fig. 2).

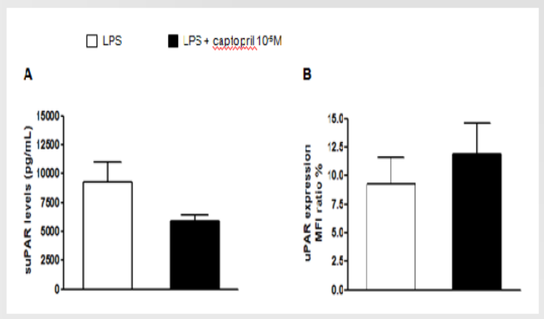
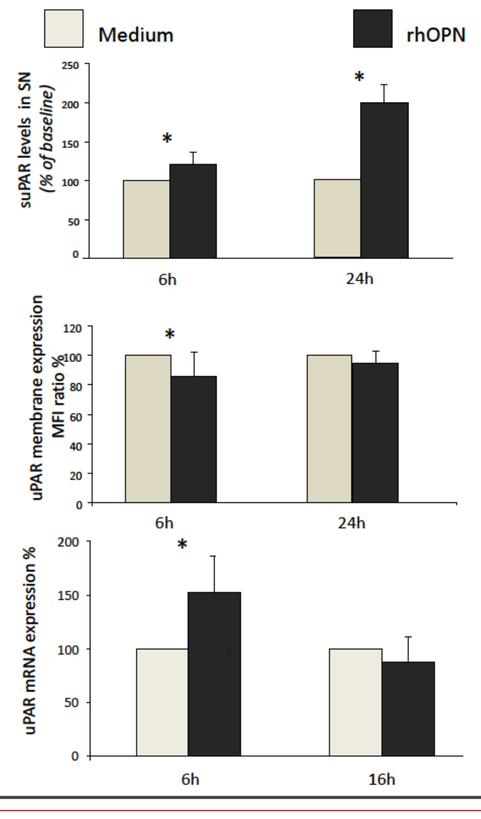


Figure 2. Effect of captopril in monocytes activated with LPS. (**A**) suPAR levels, evaluated by commercial ELISA, in culture supernatant. (**B**) MFI ratio of uPAR espression. The results are shown as mean ± standard error (SE).

Figure 3. Effect of OPN on monocytes activated with LPS.



This reduction is due to a lower cleavage from the cell's plasma membrane, as membrane-uPAR expression slightly increases after captopril exposure.

On the other side, OPN increases suPAR release from cultured monocytes through the upregulation of uPAR mRNA, but does not increase the cleavage of membrane uPAR.

DISCUSSION

SLE patients with a lupus nephritis have higher circulating suPAR and OPN levels as compared to SLE patients without renal involvement. Moreover patients with lupus nephritis on ACE-inhibitors have lower circulating OPN and suPAR levels, as well as urinary proteins.

These experiments are in keep with those clinical observations and *are consistent with a potential pathogenetic role os suPAR in lupus nephritis*: indeed suPAR might be a mediator of podocyte damage because its levels rise before the development of proteinuria.

An OPN mediated local and systemic increase of suPAR concentrations might play a significant role in the development of lupus nephritis.

Circulating (an possibly intrarenal) suPAR levels are influenced by both OPN and ACE-inhibitors, giving therefore a novel rationale for the use of ACE-inhibitors in lupus nephritis.

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