SERUM AND URINE MARKERS OF COLLAGEN DEGRADATION REFLECT RENAL FIBROSIS IN EXPERIMENTAL KIDNEY DISEASES

Marios Papasotiriou[1,2,3], Federica Genovese[4], Barbara M. Klinkhammer[3], Uta Kunter[2], Signe H. Nielsen[4], Morten A. Karsdal[4], Jürgen Floege[2], Peter Boor[2,3]

[1]University Hospital of Patras, Department of Nephrology, Patras, Greece; [2]Nephrology and Immunology and [3]Pathology, RWTH University of Aachen, Aachen, NRW, Germany; [4]Nordic Bioscience, Fibrosis Biology and Biomarkers, Herlev, Denmark.

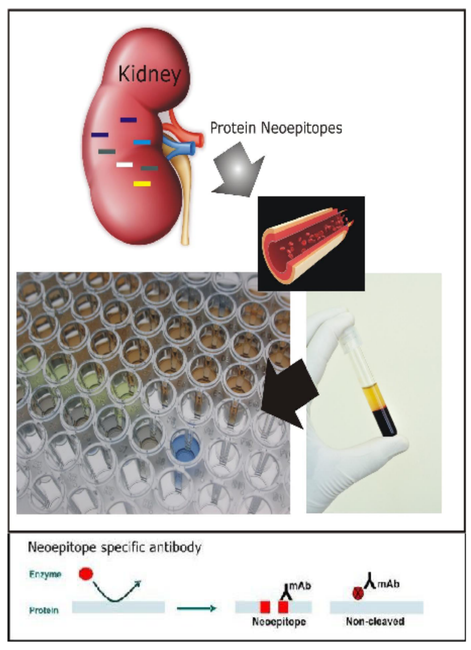
Background and aim:

In this study we explore the use of specific matrix metalloproteinase (MMP)-generated collagen degradation fragments as urinary and serological markers of fibrosis in three rat models of chronic kidney disease associated with fibrosis.

Methods:

We measured circulating and urinary, specific matrix metalloproteinase (MMP) generated collagen type I and III degradation fragments and an N-terminal propeptide of collagen III, as a marker of collagen type III production, in three rat models of kidney fibrosis: renal mass reduction (5/6 nephrectomy, n=7), progressive glomerulonephritis (chronic anti-Thy1.1 nephritis, n=6) and adenine crystal induced nephropathy (n=5). Healthy rats served as controls (n=6).

The Protein Fingerprint™ Technology



The combination of a signature protein and a pathology dependent protease results in the release of unique tissue degradation fragments that have specific neo-epitopes and are thus pathology-specific.

Protein Fingerprints™ are tissue derived biomarkers quantifiable in serum and urine.

The Biomarkers

C1M

uC1M Measured in urine — sC1M Measured in serum

C3M

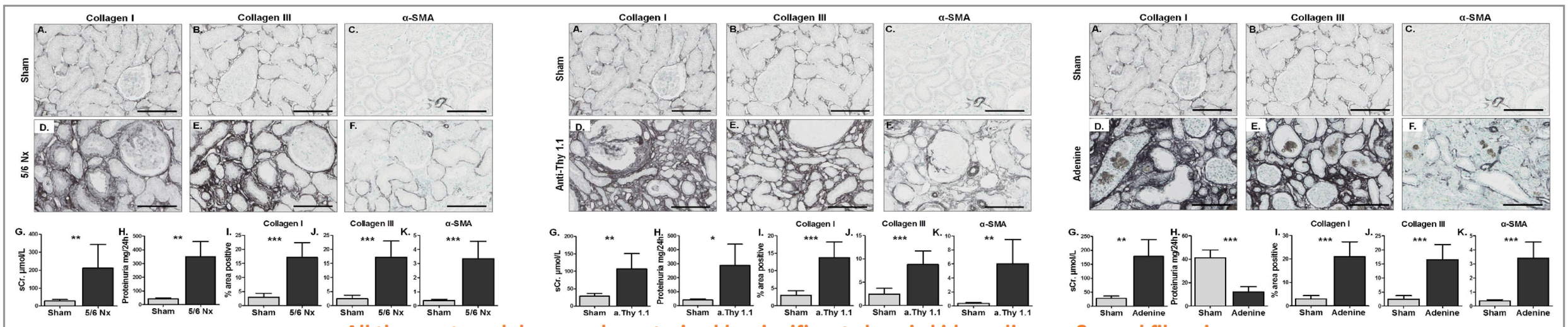
uC3M Measured in urine — sC3M Measured in serum

Pro-C3

Measured in urine and serum

Common feature of fibrosis is a dysregulated equilibrium between matrix formation and degradation. During fibrosis stages, both MMP-mediated degradation and de novo collagen synthesis are up-regulated. C1M and C3M are MMP mediated collagen type I and III degradation fragments while Pro-C3 is a marker of collagen type III *de novo* formation.

Results:



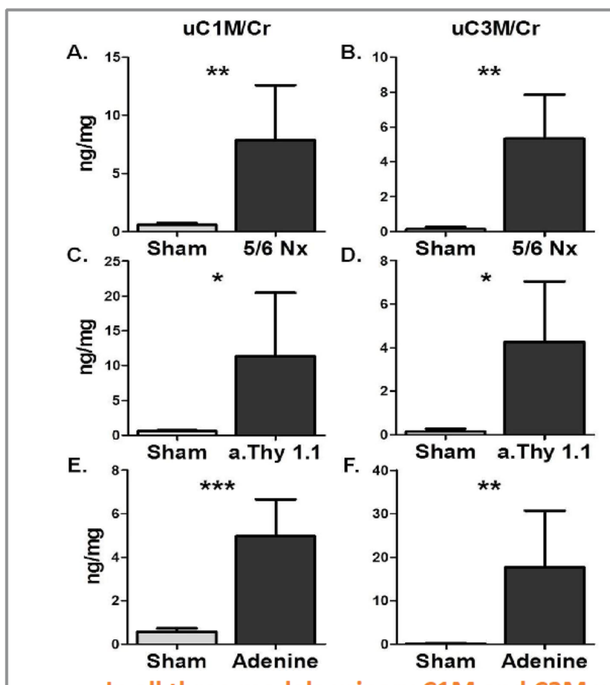
All three rat models were characterized by significant chronic kidney disease & renal fibrosis.

Renal expression of collagen type I, III and α-SMA (immunohistochemistry), serum creatinine (sCr. µmol/L) and proteinuria (mg/24h) in 5/6 nephrectomy (5/6 Nx), Anti-Thy 1.1 & adenine nephropathy vs. healthy control.

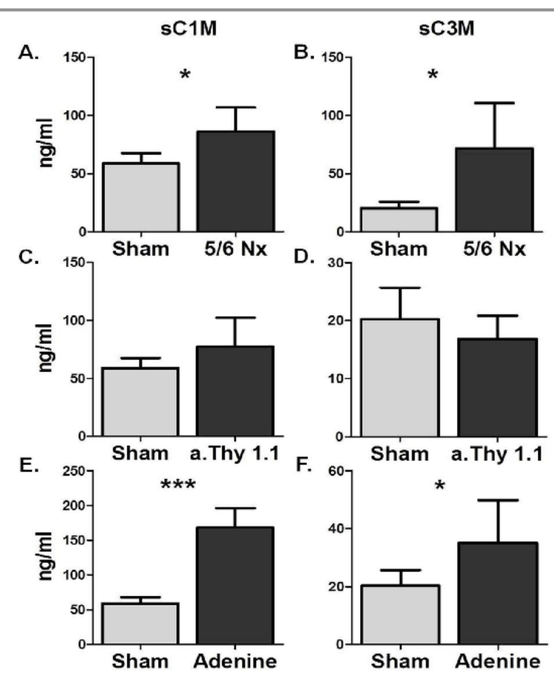
	Col. I	p	Col. III	p	α-SMA	p
Urinary C1M/Cr	**0.581**	**0.003**	**0.569**	**0.004**	**0.885**	**<0.001**
Urinary C3M/Cr	**0.675**	**<0.001**	**0.632**	**0.001**	**0.737**	**<0.001**
Urinary Pro-C3	-0.087	n.s.	0.208	n.s.	0.397	n.s.
Serum C1M	**0.511**	**0.013**	**0.551**	**<0.006**	**0.571**	**0.004**
Serum C3M	0.328	n.s.	**0.593**	**0.002**	0.271	n.s.
Serum Pro-C3	-0.034	n.s.	-0.261	n.s.	-0.377	n.s.
sCr	**0.694**	**<0.001**	**0.722**	**<0.001**	**0.688**	**<0.001**
Proteinuria	-0.140	n.s.	-0.086	n.s.	0.343	n.s.

	Proteinuria	p	sCr	p
Urinary C1M/Cr	**0.585**	**0.007**	**0.771**	**<0.001**
Urinary C3M/Cr	0.035	n.s.	**0.899**	**<0.001**
Urinary Pro-C3	**0.870**	**<0.001**	0.425	n.s.
Serum C1M	-0.235	n.s.	**0.675**	**<0.001**
Serum C3M	0.159	n.s.	**0.612**	**0.001**
Serum Pro-C3	**-0.640**	**0.014**	-0.266	n.s.

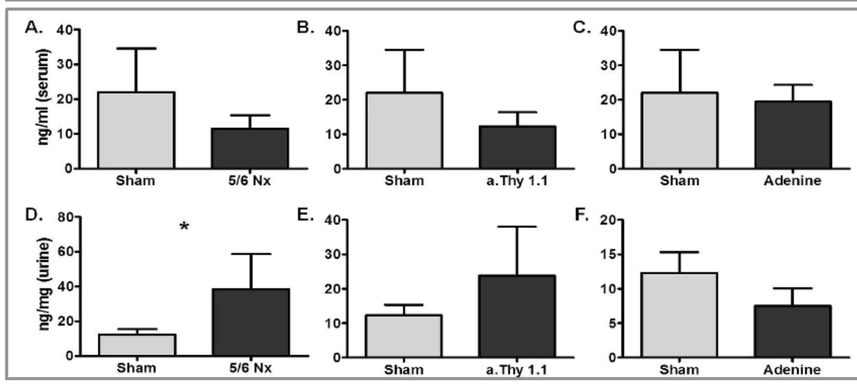
Urinary but not serum C1M and C3M correlated closely with renal fibrosis and serum creatinine.



In all three models urinary C1M and C3M were highly increased.



In serum, less pronounced increase was observed only in 5/6 Nx and Adenine nephropathy.



Serum and urinary marker of collagen type III production, N-terminal pro-peptide of collagen type III (Pro-C3), did not reflect renal fibrosis.

Conclusions:

✓ Markers of MMP-mediated collagen type I (C1M) and III (C3M) degradation in both serum and urine were increased in all animal models of renal fibrosis, in particular urinary markers (C1M and C3M) closely reflected renal fibrosis.

✓Collagen type III formation fragments (Pro-C3) did not reflect renal fibrosis.

✓**The measurement of C3M in the urine may represent a novel non-invasive diagnostic approach for kidney fibrosis.**

Contact: fge@nordicbioscience.com or pboor@ukaachen.de

www.LaBooratory.ukaachen.de

221--FP

52 ERA

J1) Chronic Kidney Disease. Lab methods, GFR measurement, urine proteomics.

Marios Papasotiriou

DOI: 10.3252/pso.eu.52era.2015

ePosters supported by F. Hoffmann- La Roche Ltd.