

H. RENAL PATHOLOGY 1

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SPECIFIC BIOMARKERS ASSOCIATED WITH ACTIVE AND CHRONIC RENAL LESIONS IN IGA NEPHROPATHY PATIENTS STRATIFIED USING THE MEST-C CLASSIFICATION. A MULTICENTER STUDY

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INTRODUCTION AND AIMS: The histologic diagnosis of idiopathic IgA Nephropathy (IgAN) is based on the “split system” where 4 types of renal lesions are scored: Mesangial hypercellularity (M 0–1), Endocapillary hypercellularity (E 0–1), Segmental glomerulosclerosis (S 0–1) and Tubular atrophy/interstitial fibrosis (T 0–2). Recently, an extension of the MEST score has been suggested introducing Crescents (C 0–2) in the split system because this lesion, together with E, are predictive of outcome (Trimarchi H et al KI, 2017). Aim of our study was to identify specific gene expression changes that characterize active renal lesions (E and C) that may be more responsive to immunosuppressive therapy than chronic lesions (S and T).

METHODS: Total RNA was extracted from archival FFPE renal tissue samples of 52 IgAN patients, 24 non-IgAN patients (minimal change disease 12, membranous nephropathy 12) and 7 kidney living donors (controls). IgAN patients were accurately stratified based on the MEST-C classifications and 4 groups were identified: 1) minimal lesions (M0,1;E0;S0,1;T0;C0); 2) active lesions (M0,1;E0,1;S0,1;T0;C0,1,2); 3) chronic lesions (M0,1;E0;S0,1;T1,2;C0); 4) mixed group (M0,1;E0,1;S0,1;T1,2;C0,1,2). Genome-wide gene expression profiles were generated and Oneway ANOVA with tukeyHSD post hoc testing was used to identify specific transcripts associated with active and chronic renal lesions in IgAN. RT-PCR was used to validate selected transcripts. Immunohistochemistry (IHC) was used to evaluate specific protein expression in biopsy specimens.

RESULTS: To Identify transcripts specifically associated with acute lesions we compared the gene expression signatures of the following groups: ACTIVE LESIONS vs CHRONIC LESIONS vs non-IgAN patients and all against KLD. Bioinformatic analysis identified 183 genes with a Fold Change > 1.5 exclusively modulated in IgAN biopsies with active lesions and 162 genes with Fold Change > 1.5 exclusively modulated in IgAN biopsies with chronic lesions. These genes belonged to renal cellular damage and immune system regulatory pathways. To establish the validity of gene expression determined by microarray analysis, we performed RT-PCR on genes that were putatively involved in generating active (*FAR2*, *DEFA4*, *TNFAIP6*) and chronic lesions (*ITGAX*, *LTB*, *CXCL6*) that may be involved in activating local inflammatory response and contributing to renal damage. Validated transcripts were also confirmed at protein level with IHC on kidney biopsy specimens.

CONCLUSIONS: Transcriptomics on FFPE renal biopsies integrates histomorphologic renal lesions. Our study identifies specific gene expression changes involved in active and chronic lesions at the time of renal biopsy. This novel information may be used for personalized therapy through a system pharmacology approach to identify targeted molecules able to revert aberrant expression networks characterizing active and chronic lesions.