

## GLOMERULAR DISEASE

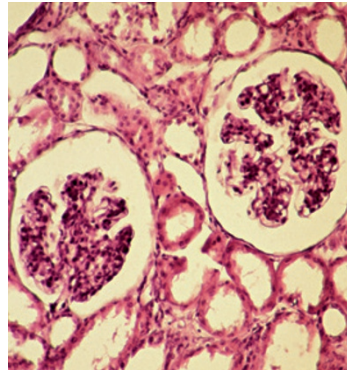
# Increased complexity of the glomerular extracellular matrix

Proteomic analyses have revealed that the glomerular extracellular matrix (ECM) is composed of many more constituent proteins than previously assumed and its organization is context dependent, according to two new studies by Rachel Lennon and colleagues from the University of Manchester, UK.

“Across the spectrum of glomerular disease we see histological changes in ECM. Whilst we associate different histological patterns with different disease processes, we have limited understanding of the changes that occur in matrix composition and the mechanisms that lead to these changes,” explains Lennon. As a first step in addressing this shortfall, the researchers used cutting-edge mass spectrometry-based proteomic techniques coupled with downstream bioinformatic analysis to define the composition of the glomerular ECM.

In the first study, the team analysed highly enriched ECM fractions of whole glomerular extracts isolated from human donor kidneys. The resulting glomerular ECM proteome consisted of 144 structural and regulatory proteins, more than twice as many as previously reported. In addition to previously identified glomerular ECM components, the researchers identified many novel proteins. Immunohistochemical co-localization studies and cross-referencing with the Human Protein Atlas resulted in the validation of more than half of the identified proteome.

In the second study, the researchers used the same techniques to investigate the contribution made to ECM production by individual glomerular cell types. Cell-derived ECM proteomes from monocultured glomerular



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endothelial cells (127 proteins) and podocytes (142 proteins) had considerable overlap with each other (55%) and with the *in vivo* glomerular ECM proteome (44%), but retained cell-type-specific differences. Co-culture of the two cell types resulted in ECM more closely resembling glomerular ECM *in vivo*, highlighting the importance of cell–cell crosstalk in the production of glomerular ECM. Protein interaction network analysis of whole glomerular ECM and glomerular cell-derived ECM revealed a common core of 35 highly connected proteins that likely have important roles in assembly and organization of the glomerular ECM.

“We have now established experimental workflows for the study of glomerular ECM that can be used to investigate developmental and disease processes,” Lennon continues. “In turn, systems-level analysis will facilitate our understanding of these processes and help to identify key regulatory pathways that can be targeted therapeutically in glomerular disease.”

*David Holmes*

**Original articles** Lennon, R. *et al.* Global analysis reveals the complexity of the human glomerular extracellular matrix. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2013030233 | Byron, A. *et al.* Glomerular cell cross-talk influences composition and assembly of extracellular matrix. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2013070795