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Targeting the Molecular Pathways of Glomerular Crescent Formation: Insights from Spatial Transcriptomics

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Objectives : Cellular glomerular crescents are a hallmark of severe glomerular injury in immune-mediated glomerular diseases. Despite their clinical significance, the molecular drivers of crescent formation in human glomeruli remain poorly understood. Identifying the transcriptional programs underlying this process could provide novel insights into autoimmune glomerular injury and potential therapeutic targets.
Methods : We employed the GeoMx Digital Spatial Profiler to analyze glomerular spatial transcriptomic signatures in crescentic glomeruli from 4 lupus nephritis (LN), 7 IgA nephropathy (IgAN), 4 anti-GBM glomerulonephritis (anti-GBM-GN), and 4 ANCA-associated glomerulonephritis (ANCA-GN) cases. Up to three whole glomeruli with overt cellular or fibrocellular crescents were selected per cases. Controls included 11 zero-time allograft biopsies, and for LN, 15 LN cases without any crescentic lesions. GeoMx DSP enables spatial transcriptomic profiling by hybridizing RNA probes to tissue sections, followed by digital quantification. Differential gene expression analysis was conducted using DESeq2.
Results : After QC, mean read count per sample ranged 30K-170K reads. Crescentic glomeruli exhibited a conserved molecular signature, characterized by upregulation of inflammation, phagosome activation, and extracellular matrix (ECM) organization pathways (e.g., SPP1, FN1, COL1A1). Conversely, anti-inflammatory and stress-response signals (DUSP1, JUN, FOS, ZFP36, KLF2, KLF9) were consistently suppressed, suggesting a maladaptive immune response contributing fibrotic remodeling. Among disease subtypes, LN exhibited the most distinct transcriptional changes, with marked upregulation of type I interferon signaling, a well-established LN-specific immunologic signature, along with apoptosis and cell adhesion pathways, implicating a unique immune-mediated injury mechanism. However, comparative DEG analysis with non-crescentic LN glomeruli confirmed that crescent formation represents a final common pathway of severe glomerular injury, rather than a disease-specific response.
Conclusions : We identified a shared molecular signature in glomerular crescent formation, linking inflammation-driven ECM remodeling and impaired stress responses to progressive autoimmune glomerular injury. These findings provide a molecular framework for crescent pathophysiology, with potential implications for targeted therapeutic interventions.

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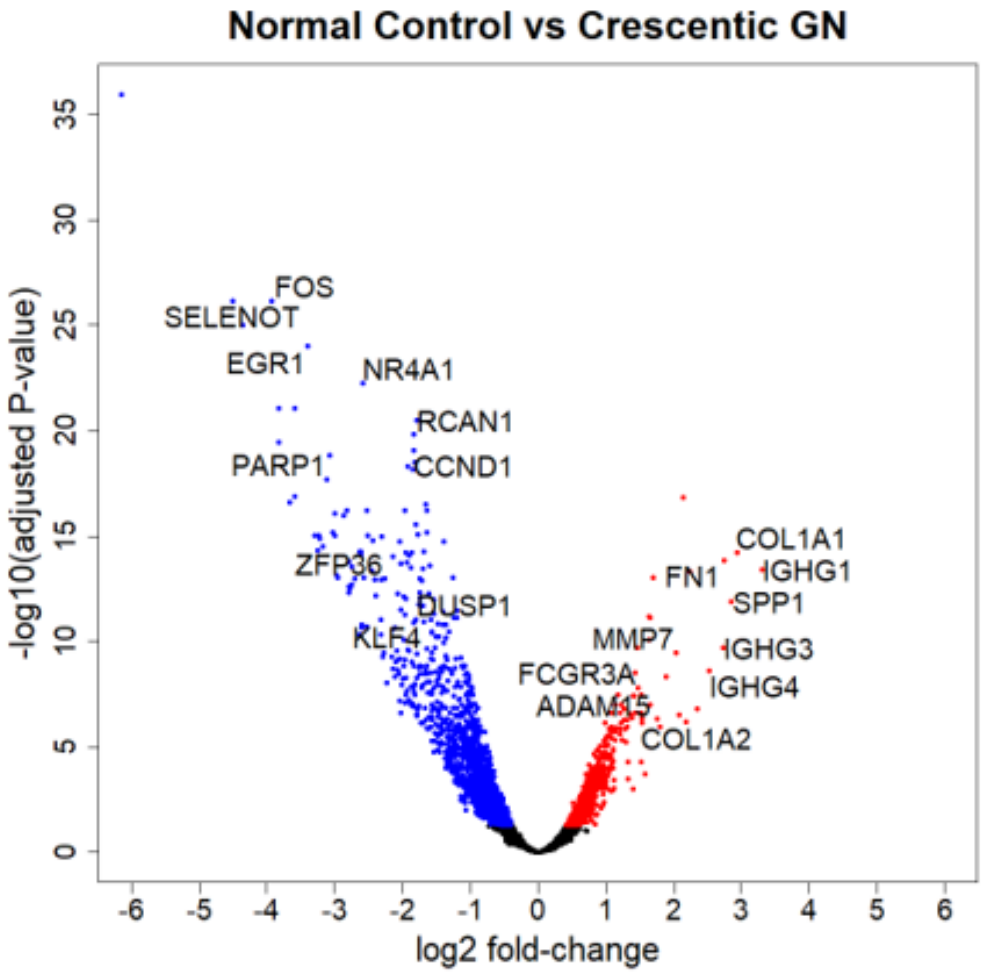

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