Glomerular Targets for Personalized Therapies in Renal Biopsies from Patients with Monoclonal Al-Light Chain-Associated Glomerulopathies. Morphology Leading the Search for Molecular Mechanisms. (Precision Medicine in Action)

G.A. Herrera[1], J. Teng[1], C. Zeng[1], L. del Pozo-Yauner[1], E.A. Turbat-Herrera[1]

[1] University of South Alabama / Whiddon College of Medicine.

Abstract

Clone therapies have improved considerably the treatment of myeloma and related entities, including monoclonal gammopathy of renal significance (MGRS) resulting in enhanced quality life expectancy. Organ-based therapies have become the next line of therapeutic intervention in patients with circulating monoclonal proteins and kidney injury. Light chain deposition disease- LCDD (monoclonal immunoglobulin deposition disease- MIDD) and AL (light chain-LC-associated) amyloidosis (AL-Am) are the main glomerulopathies that occur in these patients. It has been demonstrated that interactions between circulating monoclonal proteins and mesangial cells (MCs) are responsible for the glomerular initiation and progression in both diseases.

Five formalin-fixed paraffin embedded renal biopsies from AL-Am and 6 from LCDD patients (early to advanced) were studied using spatial transcriptomics (ST).

The enriched genes and activated cellular pathways were distinctly different. The genes activated in LCDD were RPL 41, RPS26, TNC, RP4Y1 and TGF-B engaged in matrix production leading to nodular glomerulosclerosis while in AL-Am HSP90, AB1 and HSPB1 participated in protein misfolding and aggregation. In LCDD, pathways activated supported mesangial matrix formation and in AL-Am they guided LC endocytosis, transportation to lysosomes and processing leading to fibril formation and extrusion. Variations were observed in various stages. Results validated data obtained in research platforms

Electron microscopy has played a key role in delineating pathogenesis to correlate with ST data. There are drugs in the market that can be tested in similar platforms. Establishing genes and pathways at play is a lead to novel treatments. ST allows to design individualized kidney-oriented treatments (personalized / precision medicine).