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Integrative Multi-Modal and Multi-Omics Analysis Reveals APOE–SDC2 Signaling and Macrophage Polarization as Key Drivers of Chronic Fibrosis in Kidney Xenografts

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Despite considerable advances in genetic modifications and immunosuppressive therapies, chronic xenograft injury—characterized by interstitial fibrosis and tubular atrophy—remains a major barrier to long-term kidney xenograft survival in pig-to-nonhuman primate transplantation. While M2 macrophages are known to play dual roles in tissue repair and fibrotic progression, the mechanisms by which innate immune cells, particularly activated macrophages, contribute to chronic xenograft fibrosis remain poorly understood. We conducted a comprehensive multi-modal transcriptomic approach that integrates single-nucleus RNA sequencing (snRNA-seq), spatial transcriptomics (ST), bulk RNA sequencing (bulk RNA-seq), with proteomics across multiple time points and diverse donor–recipient immunogenetic contexts. Our analysis revealed that ci (interstitial fibrosis) and ct (tubular atrophy) score escalation correlates with macrophage polarization toward pro-fibrotic lipid-associated macrophage (LAM) and M2a phenotypes, driving tubulointerstitial fibrosis progression. Spatially resolved Graph Attention–based Cell–Cell Communication analysis identified a profibrotic immune–fibroblast niche enriched near the glomerulus and arteriole, with the APOE–SDC2 axis emerging as a key mediator of macrophage–to–fibroblast communication from these regions indicating that SDC2 inhibition could be explored as a potential therapeutic target in preventing chronic xenograft injury.