Immune response after pig-to-human kidney xenotransplantation: a multimodal phenotyping study

Background

Porcine genome engineering has facilitated xenotransplantation by considerably reducing the risk of rejection. The first ever pig-to-human kidney xenotransplantations were recently performed in brain-dead human recipients. Although the xenografts remained functional during the 54h study period, and showed no signs of rejection, little was known about the immune response after the kidney transplantation. This study focused on characterizing the early immune response using a multimodal deep phenotyping approach that combined histological and immunological assessments with bulk (nCounter) and spatial (GeoMx) transcriptomics.

Research Questions

- Did standard histology capture the entire spectrum of immune injuries in xenografts?
- Would more precise phenotyping show rejection processes and tissue damage not readily apparent with standard histology?
- Is there opportunity to further refine next-generation pig constructs and optimize immunosuppressive therapies?

Results & Conclusions

- Despite favorable short-term outcomes, xenograft data suggests early signs of antibody-mediated rejection with circulating xenoantibodies and immune deposits.
- Whole transcriptome digital spatial profiling showed antibody mediated injury mainly in the glomeruli of xenografts, and was mainly associated with the involvement of monocytes, macrophages, neutrophils, and natural killer cells.
- Results suggest specific therapeutic targets towards the humoral arm of rejection to improve xenotransplantation outcomes.
- Utilizing cutting edge technologies (i.e. GeoMx spatial profiling) in a multimodal deep assessment enabled the generation of first-ever evidence of antibody-mediated rejection and the underlying biological processes driving it.

Experimental Setup

Instrument	nCounter®, GeoMx® DPS with NGS readout
Sample Type	Total RNA from biopsy specimens and matched FFPE tissue
Tissue Type	Genetically modified renal xenografts, Controls: wild-type pig kidneys, pig kidney autografts, pig kidneys with reperfusion injury
Assay	Modified nCounter® Human Organ Transplant Panel, Human GeoMx® Whole Transcriptome Atlas
Analyte(s)	RNA

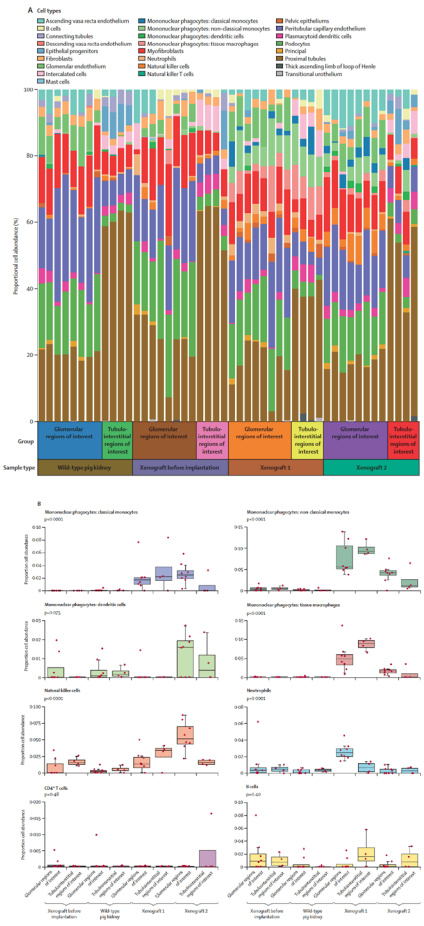

Figure 5: Spatial Cell-Type Xenografts show increase in gene expression related to humoral immune response, including monocyte and macrophage activation, natural killer cell burden, endothelial activation, complement activation and T-cell development. Reproduced with permission from Loupy et al. The Lancet 402 (10408):1158-1169 (2023)

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