Cx3cr1 Controls Kidney Resident Macrophage Heterogeneity

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Introduction: Macrophages are immune cells present within various tissues of the human body. These immune cells generally possess beneficial homeostatic roles; however, in a disease setting macrophages display varied functions, some of which may be detrimental. In polycystic kidney disease (PKD), kidney macrophages are thought to promote the rate of cyst expansion and disease progression. It is known that kidney macrophages are comprised of both monocyte-derived and tissue resident populations; however, the heterogeneity of kidney macrophages and factors that control their heterogeneity are poorly understood.

Methods: To explore the cellular heterogeneity of kidney macrophages, we performed single cell RNA sequencing (scRNAseq), fate mapping, genetic knockout, and parabiosis studies on healthy C57BL6/J wild type and conditional ciliopathy (*Ift88*) mice.

Results: Our data indicate that healthy mouse kidneys contain four major subsets of monocyte-derived macrophages and two major subsets of kidney resident macrophages (KRM) including a population with enriched *Ccr2* expression, suggesting monocyte origin. Surprisingly, fate mapping data using the newly developed *Ms4a3*^{Cre} *Rosa Stop*$^{f/f}$ *TdT* model indicate that less than 50% of *Ccr2*$^{+}$ KRM are derived from Ly6c^{hi} monocytes. Instead, we find that *Ccr2* expression in KRM reflects their spatial distribution as this cell population is almost exclusively found in the kidney cortex. We next identify a gene, *Cx3cr1,* that governs cortex specific accumulation of *Ccr2*$^{+}$ KRM. By using a *Cx3cr1* knockout mouse, we show that loss of *Ccr2*$^{+}$ KRM reduces the severity of PKD in a conditional ciliopathy (*Ift88*) mouse model where cysts are mainly localized to the kidney cortex.

Conclusions: KRM heterogeneity is driven by spatial distribution and identify a gene, *Cx3cr1,* that is critical for regulating this spatial distribution and niche-specific PKD progression.

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