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Regulation of Bacterial Load in Leptospira-Infected Macrophages through IL-10: Significance for Leptospirosis Kidney Diseases

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Objectives : Macrophages, a heterogeneous population of innate immune cells, emerge as the predominant infiltrating phagocytes in Leptospira-infected kidneys. Leptospira spp. colonizing renal tubules are implicated in the progression of leptospirosis kidney diseases. Previous studies have shown that pathogenic L. interrogans, but not nonpathogenic L. biflexa, can survive, replicate, and escape from macrophages. However, the mechanisms by which this pathogenic Leptospira spp. escapes from macrophages to establish renal colonization remain unclear.
Methods : 1. Investigating the transcriptomic profile of infected macrophages using single-cell RNA sequencing technologies to discern differences between pathogenic and nonpathogenic Leptospira infections. 2. Investigating the impact of IL-10 on macrophages and kidneys infected with Leptospira.
Results : The single-cell RNA sequencing analysis included a total of 5,717 cells, with 2,552 cells from pathogenic leptospiral-infected cells and 3,165 cells from nonpathogenic leptospiral-infected cells. Following infection, four distinct subpopulations of activated macrophages were identified: Cluster 0 (Antigen presentation), Cluster 1 (Inflammation and Migration), Cluster 2 (Metabolism and Immune homeostasis) and Cluster 3 (Unknown). Pathogenic Leptospira predominantly induced Cluster 0, while nonpathogenic Leptospira primarily induced Cluster 2. A subpopulation (Cluster 0 marked by IL-10) with elevated IL-10 levels was exclusively observed in nonpathogenic Leptospira-infected macrophages. CellChat program analysis highlighted that IL-10 signaling pathways in Cluster 0 are from nonpathogenic Leptospira-infected macrophages. Knockdown of IL-10 in macrophages increased intracellular Leptospira quantity, emphasizing the role of IL-10 in controlling Leptospira load during the host's defense. Neutralizing IL-10 in Leptospira-infected mice resulted in increased leptospiral burdens in the infected kidneys.
Conclusions : Our study reveals the protective role of IL-10 in the host's defense against leptospiral infection. This research provides a comprehensive understanding of gene expression alterations in pathogenic and nonpathogenic Leptospira-infected macrophages, shedding light on host cell population dynamics during infection and may pave the way for the development of new therapeutic strategies.

Table 1.png

Cluster	Macrophage Genes	Additional Defining Genes	Putative Classification
MC0	*Adgre1*$^{+}$*Itgam*$^{+}$ *Cd14*^{LO}*Cd68*^{LO}	*Fgd2; Tmem176b; Aif1*	Antigen presentation
MC1	*Adgre1*$^{+}$*Itgam*$^{+}$ *Cd14*$^{+}$*Cd68*^{LO}	*Sema3c; Glipr2; Mmp8*	Inflammatory; migration
MC2	*Adgre1*^{LO} *Itgam*^{LO} *Cd14*$^{+}$*Cd68*$^{+}$ *Itgax*$^{+}$	*Atp6v0d2; Angptl2*	Inflammatory; Metabolic homeostasis; Lipid-associated
MC3	*Adgre1*^{LO} *Itgam*^{LO} *Cd14*^{LO} *Cd68*^{LO}	-	Other

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