TABLE 1. The applications of scRNA-seq in infection.

Pathogen	Host/cell	Cell isolation	scRNA-seq method/platform	Key findings	Ref.
S. Typhimurium	Mouse/Bone-marrow-derived macrophages (BMDMs)	FACS	SMART-seq	The induction of macrophage type I IFN response was correlated with the variable PhoPQ activity of invading bacteria.	[19]
	Mouse/BMDMs	FACS	Smart-seq2	Macrophages harboring non-growing *Salmonella* displayed proinflammatory M1 polarization state while macrophages containing growing bacteria turned into an M2-like anti-inflammatory expression program.	[20]
	Mouse/BMDMs	FACS	CEL-Seq2	Development of scDual-seq, that captured host and pathogen transcriptomes simultaneously.	[22]
	Human/Monocyte-derived dendritic cells (MoDCs)	FACS	SMART-seq2	Invasive *Salmonella* strain ST313 exploited discrete evasion strategies within infected and bystander MoDCs to mediate its dissemination *in vivo*.	[21]
	Human/PBMCs	FACS	10xGenomics	Development of a deconvolution algorithm for inferring cell-type specific infection responses from bulk measurements.	[98]
M. tuberculosis	Human/PBMCs	FACS	10xGenomics	Revealed a gradual depletion of a NK cell subset from HC LTBI and active TB.	[26]
	Human/Monocyte-derived macrophages (MDM)	Microwell	Seq-Well	Development of the Seq-well method and revealed distinct heterogeneity between macrophages exposed and unexposed to Mtb.	[24]
SARS-CoV-2	Human/*M. mulatta*/ *M. fascicularis*/ Mouse/multiple tissues, e.g., lung, ileal, nasal	Microwell Droplets Microfluidic	Seq-Well Drop-Seq 10xGenomics	Identified ACE2 and TMPRSS2 co-expressing cells within lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells. Discovered that ACE2 was a human ISG *in vitro*.	[38]
	Human/ Bronchoalveolar lavage (BAL) samples	FACS Microfluidic	MARS-seq 10xGenomics	Development of the Viral-Track method to scan for viral RNA in scRNA-seq data and revealed the infection landscape of mild and severe COVID-19 patients.	[40]
	Human/A549 cells, Primary human bronchial epithelial cells	Microfluidic	ECCITE-seq 10xGenomics	Combined CRISPR screen with scRNA-seq, identified new host factors required for SARS-CoV-2 infection, increased cholesterol biosynthesis were related to reduced infection.	[49]
	Human/$CD4^+$ T cells	Microfluidic	10xGenomics	Hospitalization was associated with increased cytotoxic Tfh and cytotoxic T helper cells and a reduction in regulatory T cells.	[45]
	Human/PBMCs	Microfluidic	10xGenomics	Aging induced the dysregulation of the immune system and increased gene expression associated with SARS-CoV-2 susceptibility.	[104]
	Human/B cells	Microfluidic	10xGenomics	Identified potent neutralizing antibodies from convalescent COVID-19 patients.	[50]

TABLE 1 (continued). The applications of scRNA-seq in infection.

Pathogen	Host/cell	Cell isolation	scRNA-seq method/platform	Key findings	Ref.
Influenza	Mouse/Lung	FACS	MARS-seq	Analyzed viral and host transcriptomes in the same single cell and revealed cellular heterogeneity and novel markers specific for influenza-infected cells.	[105]
	Human/A549 cells	Microfluidic	10xGenomics	Infections performed at high MOIs resulted in increased viral gene expression per cell and IFN lambda 1 (IFNL1) showed a widespread pattern of expression more reliant on paracrine signaling.	[106]
	Human/A549 cells	Microfluidic	10xGenomics	Demonstrated the intricate effects of defective viral genomes on host transcriptional responses.	[107]
	Mouse/Lung	Microfluidic	10xGenomics	Demonstrated that two waves of pro-inflammatory factors were released during IAV infection.	[54]
HIV	Human/$CD4^+$ T cells	Microfluidic	Fluidigm C1	Cell state driven by T-cell receptor mediated cell activation was the main factor of transcriptional heterogeneity and was tested as a biomarker of HIV permissiveness.	[108]
	Human/$CD4^+$ T cells	Microfluidic	10xGenomics	Expression of HIV proviruses within the latent reservoir were influenced by the host cell transcriptional program.	[109]
	Human/$CD4^+$ T cells	Microfluidic	Fluidigm C1	Characterized cell heterogeneity during HIV latency and reactivation and identified transcriptional programs leading to successful reactivation of HIV expression.	[110]
	Human/PBMCs	Microwell	Seq-Well	Characterized multiple dynamic cellular responses and gene expression modules that varied by time and cell subsets during acute HIV infection.	[53]
Zika virus	Human/Neuroepithelial Stem Cells(NES cells)	Microfluidic	Fluidigm C1	Zika virus (ZIKV) infected NES cells and radial glia cells and induced mitochondrial sequestration of centrosomal phospho-TBK1, nucleoside analogs inhibited ZIKV replication.	[111]
	Human/Developing cortex	Microfluidic	Fluidigm C1	AXL was a candidate Zika entry receptor in neural stem cells and its expression was conserved in rodents and human cerebral organoid model systems.	[112]
	Mouse/Neuronal stem cells(NSCs)	Microfluidic	10xGenomics	Generated a fully immunocompetent mouse model of ZIKV infection and the NS4B G18R mutation in ZIKV likely acted through its ability to diminish IFN-β levels.	[113]
Dengue virus	Human/PBMCs	FACS	Smart-seq2	Identified cells with viral RNA from human patients and studied the molecular signatures preceding the development of severe dengue infection.	[114]

TABLE 1 (continued). The applications of scRNA-seq in infection.

Pathogen	Host/cell	Cell isolation	scRNA-seq method/platform	Key findings	Ref.
Ebola virus	Rhesus monkeys/ PBMCs	Microwell	Seq-Well	Demonstrated that the EBOV tropism, replication dynamics, and elicited immune responses were mediated by viral infection related to cytokine signaling.	[115]
P. chabaudi	Mouse/$CD4^+$ T cells	FACS Microfluidic	SmartSeq-2 Fluidigm C1	Reconstructed the developmental trajectories of Th1 and Tfh (T follicular helper) cells during blood-stage *Plasmodium* infection.	[70]
	Mouse/$CD4^+$ T cells	FACS	Fluidigm C1	$CD4^+$ T cell-derived MCSF regulated expansion and activation on of specific myeloid subsets.	[71]
P. falciparum	Human/B^+ erythrocytes	Microfluidic	Fluidigm C1	Discovered undefined sex-specific genes as well as three distinct clusters of late-stage asexual parasites largely defined by stage-specific genes.	[116]
	Human/RBCs	Droplets	Drop-seq	Revealed the gene expression signature of sexual commitment that AP2-G^+ mature schizonts specifically upregulated additional epigenetic regulators.	[60]
P. falciparum *P. berghei*	Mouse, Human/Red blood cells (RBCs)	FACS	Smart-seq2	Observed sharp transcriptional transitions at the asexual stage and discovered a set of sex-specific genes involved in sequestration of mature gametocytes.	[61]
P. falciparum *P. berghei* *P. knowlesi*	Human/RBCs	FACS Microfluidic	SMART-seq2 10xGenomics	Assembled a Malaria Cell Atlas that presented the transcriptomic profiles of individual *Plasmodium* parasites across all morphological life cycle stages.	[65]
Trypanosoma brucei	*Glossina morsitans morsitans*/salivary glands	Microfluidic	10xGenomics	Described proteins associated with the different parasite developmental stages in salivary glands and highlighted a family of nonvariant surface proteins associated with metacyclic parasites.	[117]
Toxoplasma	Human/Monocytes	Microfluidic	10xGenomics	Revealed that $CD14^+CD16^-$ monocytes were key regulators of human monocyte transcriptional response to *Toxoplasma*.	[118]
C. albicans	Human/PBMCs	Microfluidic	10xGenomics	Integrated GWAS with bulk and scRNA-seq, identified 27 *Candida*-response QTLs and revealed a role for *LY86* in the anti-*Candida* host response.	[77]

Abbreviations: *P. knowlesi*: *Plasmodium knowlesi*; FACS: Fluorescence-Activated Cell Sorting; GWAS: Genome-Wide Associated Studies; HC: healthy control; IAV: Influenza A virus; ISG: Interferon-Stimulated Gene; LTBI: latent TB infection; MCSF: Macrophage Stimulating Factor; *M. fascicularis*: *Macaca fascicularis*; *M. mulatta*: *Macaca mulatta*; MOI: Multiplicity Of Infection; Mtb: *Mycobacterium tuberculosis*; NK: natural killer; PBMCs: Peripheral Blood Mononuclear Cells; *P. berghei*: *Plasmodium berghei*; *P. chabaudi*: *Plasmodium chabaudi*; *P. falciparum: Plasmodium falciparum*; *P. knowlesi*: *Plasmodium knowlesi*; QTL: Quantitative Trait Loci; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2; TB: tuberculosis.