Murine gammaherpesvirus 68 efficiently infects myeloid cells resulting in atypical, restricted form of viral infection

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Murine gammaherpesvirus 68 (MHV68) has been reported to infect myeloid cells both during primary infection and latency. Previous studies have identified factors that can enhance virus replication in these cells, but the nature of MHV68 infection in myeloid cells still remains poorly characterized. Here, we have taken two parallel tracks to investigate virus-macrophage interactions during primary infection using a highly sensitive MHV68 reporter virus that enables single-cell analysis of virus infection. This virus demonstrated that MHV68 is capable of infecting a macrophage cell line comparably to a fully permissive fibroblast cell line, but MHV68-infected macrophages show significantly delayed expression of immediate early, early and late genes, impaired viral DNA synthesis and limited lytic protein induction. In parallel, we harvested macrophages at 16 hours after in vivo MHV68 infection and analyzed gene expression by single cell RNA-seq. This analysis identified that early MHV68 infection of macrophages in vivo is primarily focused in one subset of macrophages, with limited infection and gene expression in a second, transcriptionally distinct macrophage subset. Among all virally infected cells, ongoing virus replication was only observed in rare (0.25%) cells. In contrast, scRNA-seq demonstrated that 13% of MHV68-infected macrophages had detectable LANA mRNA, a marker of latent virus infection, and ~50% of cells expressed ORF75a, ORF75b and/or ORF75c, three closely related viral genes more commonly associated with ongoing virus infection. We found this unusual viral transcription program also occurred in MHV68 infection of a macrophage cell line. In total, these studies indicate that entry and early steps in MHV68 infection of macrophages are efficient, yet subsequent infection is characterized by a state of atypical, restricted viral transcription.