#39: Systemic, rather than local, macrophages limit virus spread following an intradermal infection

Nick J. Parekh, Michael L. Davies, Irene E. Reider, Tracy E. Krouse, Chetna Soni, Lauren W. Kaminsky, Matthew A. Fischer, Nico van Rooijen, Ziaur SM Rahman, Chris C. Norbury

Following a peripheral virus infection, the immune system activates a robust response in an effort to limit virus dissemination and prevent or reduce systemic spread. It is the initial actions of the innate immune response, matched against the pace of virus replication, that are important for mediating a successful outcome for the host. The poxvirus, Vaccinia virus (VACV), is restricted from causing systemic disease, but the precise mechanism of preventing systemic virus dissemination following a peripheral infection remains poorly understood. It is critical to understand the mechanisms that prevent systemic dissemination of viruses that spread via the lympho-hematogenous route after a peripheral infection, such as; measles, mumps, dengue, and many others of importance to human health.

Uninhibited, poxviruses spread from the site of infection through the draining lymph node to the spleen and liver, and from these tissues virus particles further spread systemically through the blood. Immune cells recruited to the site of infection or cells resident within the draining lymph node are widely considered to restrict the spread of many viruses. However, our recent work suggests that systemic, rather than local, populations of macrophages are responsible for preventing widespread dissemination of replicating VACV following intradermal infection. Utilizing various cell-depletion methods, we found that systemic depletion of macrophages allows for VACV spread to the ovaries, an assay for unrestricted spread. Further, when depletion of macrophages was limited to the site of infection or the draining lymph node, VACV was unable to reach the ovaries, suggesting that cells within these tissues are not required to prevent virus spread. However, systemic macrophage depletion was no longer sufficient to allow virus spread when depleted more than 4 days after infection, indicating that after 4 days, it is likely that a recruited cell type is able to prevent spread of VACV from the peripheral site of infection. Our data indicate that two populations of marginal zone macrophages are primary targets of VACV infection in the spleen, and depletion of these cells allows widespread virus dissemination. Therefore, we show that the level of virus control is not the site of infection or draining lymph node, but is likely via infection of macrophage populations in the spleen that do not allow productive replication of VACV and may trigger further innate and adaptive immune responses.