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A novel population of myeloid cells responding to coxsackievirus infection in the neonatal CNS nxpress a neural stem cell marker

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Enterovirus infection in newborn infants is a significant cause of aseptic meningitis and encephalitis. Using a neonatal mouse model, we previously determined that coxsackievirus B3 (CVB3) preferentially targets proliferating neural stem cells located in the subventricular zone within 24 hours after infection. At later time points, immature neuroblasts, and eventually mature neurons, were infected as determined by expression of high levels of viral protein. Here, we show that blood-derived mononuclear cells were rapidly recruited to the CNS within 12 hours after infection with CVB3. These cells displayed a myeloid-like morphology and were highly susceptible to infection during their recruitment into the CNS. Kinetic data from serial immunofluorescence images captured the extravasation of infected myeloid cells through the choroid plexus epithelium, and their eventually penetration into the parenchyma of the brain. Prior to their migration through the ependymal cell layer (ECL), a subset of these infected myeloid cells expressed detectable levels of nestin, a marker for neural stem cells. Nestin$^+$ myeloid cells infected with CVB3 underwent diapedesis through the ECL and revealed distinct morphological characteristics typical of type B neural stem cells. The recruitment of these novel myeloid cells may be specifically set in motion by chemokine induction in the CNS following early CVB3 infection. In order to investigate this phenomenon, we performed an Illumina BeadArray Whole Mouse Genome analysis of the neonatal brain following infection with two contrasting RNA viruses in hopes of identifying novel chemokines and cytokines induced specifically by CVB3 infection. We propose that CVB3 infection may lead to the recruitment of these blood-derived myeloid cells into the CNS, thereby contributing to the repair process during virus-mediated pathology. In turn, the proliferative and metabolic status of these recruited myeloid cells may render them attractive targets for CVB3 infection. Moreover, the migratory ability of myeloid cells may point to a productive method of virus dissemination in the CNS.

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