MCP-3 AS A KEY INITIATOR OF MONOCYTE INFILTRATION INTO THE SIV-INFECTED BRAIN.


Monocytes traffic through the brain as part of routine surveillance; this activity is increased during HIV infection in humans, and SIV infection in Rhesus macaques. HIV/SIV encephalitis (HIV/SIVE) is defined by perivascular accumulation of macrophages, and the formation of multinucleated giant cells. Specific chemokines responsible for recruiting monocytes into the brain during SIV infection have not been identified previously.

Cultured astrocytes were exposed to differing levels of TNF-α for 48 hours before being analyzed for changes in monocyte chemotactic protein 3 (MCP-3) production and secretion. Gene array data showed MCP-3 was upregulated more than any other chemokine analyzed. Immunofluorescence showed that astrocytes were actively secreting MCP-3 following TNF-α stimulation.

Additionally, astrocyte conditioned media were used to induce migration of peripheral blood mononuclear cells (PBMCs) across transwell filters. Increased migration of PMBCs was seen in when media from TNF-α treated astrocytes was used, compared with control astrocyte media. This increased migration was mitigated by pre-incubation of astrocyte media with a recombinant blocking antibody.

Ex vivo experiments were performed by incubating brain slices with control or SIVmac251 infected macrophages for 4 hours. MCP-3 positive vesicles were seen in astrocyte processes (shown by co-labeling with GFAP) when SIV-infected macrophages were used, this was not seen in control slices.

Our data indicate that MCP-3 may be a leading chemokine in recruiting monocytes into the brain during early HIV/SIV infection.