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Implication of macrophages in blood brain barrier disruption during central nervous system infection

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Infection of the central nervous system (CNS) with the neurotropic JHM strain of mouse hepatitis virus (JHMV) induces extensive cell infiltration and provides a useful model to study both virus-induced encephalitis and demyelination. Cells recruited into the CNS include components of the innate response, namely neutrophils, NK cells and macrophages, followed by CD4, CD8 T cells and B cells. CD8 T cells are the primary effectors which control virus replication. The exact contribution of macrophages in JHMV pathogenesis remains unclear. Pathogenesis studies in CCR5 deficient mice (a chemokine receptor involved in macrophage and T cell recruitment) suggested a role of macrophages in demyelination. In addition, depletion of both neutrophils and monocytes by the anti-Gr1 antibody (RB6-8C5) significantly reduced blood brain barrier (BBB) permeability and correlated with an absence of matrix metalloproteinase-9 (MMP9) activity. These data suggested a potential role of neutrophils and macrophages in BBB disruption by MMP9 release.

To specifically assess the contribution of macrophages in BBB breakdown, JHMV pathogenesis was analyzed in CCL2 deficient ($CCL2^{-/-}$) mice. Infected $CCL2^{-/-}$ mice showed a delay in clinical disease compared to wt mice, which correlated with a significant decrease of CNS leukocyte infiltration at early time points. This decrease was mainly due to very limited $F4/80^{+}$ macrophage infiltration, indicating an important contribution of CCL2 in macrophage migration to the CNS. Nevertheless, CNS recruitment of CD4 and CD8 T cells in $CCL2^{-/-}$ mice was similar to wt mice, demonstrating that neither CCL2 nor macrophages are essential for CNS T cell infiltration during JHMV infection. But despite similar T cell recruitment, control of virus replication was delayed in mice lacking CCL2 compared to wt mice. In addition, sodium fluorescein i.p. injection showed a reduction of BBB permeability in $CCL2^{-/-}$ mice during the acute phase of infection. However, MMP9 activity was increased in $CCL2^{-/-}$ mice compared to controls and correlated with elevated and prolonged neutrophil retention in the CNS. These data demonstrate an MMP9 independent role of monocytes in enhancing BBB permeability during acute viral encephalitis and suggest CCL2 as a potential target to reduce leukocyte infiltration during CNS inflammatory disorders.

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