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Editorial

# The Role of Monocyte Chemoattract Protein-1 in Acute Ischemic Stroke and Chronic Alzheimer Disease

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A subset of infiltrating peripheral monocytes is known to be recruited to CNS by monocyte chemoattractant protein-1 (MCP-1/CCL2) signaling in various neurological diseases. We have recently reported striking switch in the activation phenotype and population of mononuclear phagocytes from resident microglia to infiltrating macrophages in neuronal cell death induced CCL2 dependent manner in a mouse model which overexpressed Tau-Tubulin Kinase-1 (TTBK1) [1].Although TTBK1 up regulation is detected in brains of human Alzheimer's disease (AD), this dramatic conversion of the cell population from microglia to pro-inflammatory M1-skewed infiltrating monocytes are well characterized in the patients with acute stroke. In this short communication, I introduce the role of CCL2 in macrophage filtration to affected region of the acute is chemic stroke and AD brain.

In our TTBK1 overexpression mice, danger-associated molecular pattern molecules (DAMPs, such as ATP, DNA, S100, and chromatin-associated molecules released from injured neurons) activate pro-inflammatory M1-like innate immunity response of mononuclear phagocytes and CCL2 production. This leads to the recruitment of peripheral macrophages into the affected brain region and acceleration of neuronal cell death via bystander killing of neurons. Infiltrating macrophages are known to serve as a key mediator of the innate immune response by their expression of Toll-like receptors (TLRs) and activation of TLRs of macrophages leads to the secretion of pro-inflammatory cytokines. In post-ischemic inflammation, the central event is also recruitment of leukocytes, first neutrophils, and then an influx of cells of the monocyte/macrophage lineage. Experimentally, CCL2 overexpression increases the infarct volume and monocytes and macrophages invasion of the ischemic area [2]. In contrast, CCL2-deficient mice are resistant to permanent middle cerebral artery occlusion [3] and the expression by gene transfer of dominant negative CCL2 in the post-ischemic period in hypertensive rats reduced the infarct volume and leukocyte infiltration [4]. In the human AD brain, increased expression of pro-inflammatory cytokines or chemokines is accompanied by M1-skewed microglial activation. Additionally, CCL2 levels are known to be associated with cognitive decline during the early stage of AD patients [5-8]. These findings are reproduced in several AD mouse models such as the APP+PS1 mouse [9], which shows a distinctive age-dependent shift from M2 (anti-inflammatory) to M1 (pro-inflammatory) mononuclear cell activation in the hippocampus.

Taken together, CCL2 and its receptor CCR2 should be important targets in the development of treatments to fight or prevent acute and chronic neurological disorders in which neuroinflammation is a pathological key event.

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