TLR4-activated p38 and NF-κB and GM-CSF receptor-mediated JAK2/STAT5 pathways are important for microglial long-term survival

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We have previously reported that the activation of Toll-like receptor 4 (TLR4) by lipopolysaccharide (LPS) induced rapid death of primary cultured rat microglia. However, a subpopulation of microglia survived much longer than two days, in which time all control cells had died. These surviving microglia may have neuroprotective functions because the neurons remained viable in co-cultures with these microglia. Moreover, the LPS-stimulated microglia may produce GM-CSF to promote survival. However, signaling mechanism of TLR4-mediated microglial long-term survival remains unknown. Therefore, in this study, we investigated TLR4 signaling pathways that control microglial survival, focusing on p38 MAP kinase and NF-κB, which are known to be important for innate immune response and control of apoptosis. Furthermore, we examined the involvement of GM-CSF receptor downstream signaling intermediates, JAK2 and STAT5, which are known to regulate the transcription of survival genes. LPS stimulation resulted in the phosphorylation of p38 MAP kinase, NF-κB and STAT5 in primary rat microglia. Moreover, a p38 MAP kinase inhibitor, SB202190, and a NF-κB inhibitor, BAY11-7082, suppressed LPS-stimulated microglial survival. Inhibition of JAK2 by NVP-BSK805 also inhibited the survival of these microglia. These results suggest that p38 and/or NF-κB pathways may play important roles in TLR4-mediated microglial survival. Furthermore, microglia-producing GM-CSF may activate cytoprotective JAK2/STAT5 signals to support their survival.