Pathogen mimetics activate MAP kinase signalling and induce inflammatory molecules in microglia

Jaedeok Kwon(j.kwon.1@research.gla.ac.uk)
University of Glasgow

Abstract

The aetiology of Schizophrenia remains uncertain. One hypothesis is that maternal immune activation may play a role potentially via action on neurones or microglia. Additionally, some of the high risk genetic factors are related to immunity. A number of studies have shown increased levels of microglial activity in patient brain, elevated cytokines and chemokines in serum. Mitogen-activated protein (MAP) kinase signalling has been genetically linked to schizophrenia. In this study, the ability of immune mimetics to activate MAP kinases and to induce immune responses in microglia was tested.

A mouse microglial cell line, SIM-A9 (1), was exposed to LPS (50 ng/ml), poly I:C (100 ng/ml) or resiquimod (R848, 3 uM) for required stimulation time. Protein was extracted and levels of phosphorylated MAP kinases (pERK, pJNK and pp38) were measured by Western blot. Via RT-qPCR, chemokines (Ccl5 and Cxcl10) were measured.

R848 activated all pMAP kinases in the cells, however, no significant response was detected to LPS and poly I:C at a short exposure time. With LPS, increased levels of pJNK an after 30 min. In contrast to LPS, poly I:C did not show any significant changes at a longer exposure time.

Ccl5 and Cxcl10 were induced significantly by LPS for 8 and 24 h (but not 30 min) compared to control. R848 also increased Ccl5 at 8 and 24 h, however Cxcl10 induction showed a different temporal profile - only elevated at 30 min and 8 h with. Again, poly I:C stimulation did not show any significance in both genes.

These findings suggest that SIM-A9 use MAPK pathway for R848 and LPS induced stimulation. Moreover, two mimetics induce inflammatory chemokines which can damage neuronal networks in the brain. In conclusion, because of induced MAP kinase phosphorylation, MAP kinases can have important roles in microglial immune response signalling cascades, and this may be relevant to schizophrenia aetiology.

Keywords: *Microglia, Schizophrenia, prenatal inflammation, cytokines, MAPKs*

References

[1] Nagamoto-Combs K, Kulas J, Combs CK. A novel cell line from spontaneously immortalized murine microglia. Journal of neuroscience methods. 2014;233:187-98.

Biography

I am a Ph.D. candidate at the University of Glasgow. I received MRes in Biomedical science from the University of Glasgow. My current interests include the role of the JNK pathway on the schizophrenia-relevant neuroimmunological changes in microglia after immune challenges during pregnancy, including responses of chemokines, cytokines and their receptors' expression profiles