Fstl1 mediates polyI:C-induced neuronal impairment.

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Viral infection in perinatal period may affect early brain development, which increases the risk for psychiatric disorders such as schizophrenia. Our previous findings showed that polyriboioinic-polyribocytidylic acid (polyI:C) treatment in neonatal mice, which mimics virus infection by inducing innate immune system, leads to behavioral abnormality in adulthood. Furthermore, polyI:C treatment induces the expression of interferon-induced transmembrane protein 3 (Ifitm3) in astrocytes but not neurons. Ifitm3 may mediate polyI:C-induced neuronal impairment through the induction of humoral factors secreted from astrocytes. However, it remains unknown which molecular entity leads to the neuronal impairment. We screened humoral factors secreted from astrocytes by proteomic approach. As a result, we identified Follistatin like-1 (Fstl1) as a candidate astroglial factor. Astrocyte condition medium (ACM) from secondary cultured astrocytes treated with polyI:C contained a significantly higher amount of Fstl1 protein than the level in control ACM. Increase in Fstl1 level by polyI:C treatment was not observed in astrocytes from Ifitm3 KO mice. Treatment of recombinant Fstl1 on primary cultured neurons induced an impairment of neurite elongation, whereas, knockdown of Fstl1 in astrocytes diminished the neuronal impairment caused by treatment with ACM. These results suggest that astrocyte-derived Fstl1 plays a crucial role in polyI:C-induced neuronal impairment.