Reduction of α-synuclein spreading via targeting TLR2/MyD88/NF-kB pathway

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Objective:
Spreading of pathological α-synuclein (α-syn) and concomitant induction of inflammation is well manifested in brains of Parkinson's disease (PD), Multiple system atrophy (MSA) and Lewy Body Dementia (LBD). Inflammation and α-syn spreading are found to positively facilitate each other, but the mechanism of crosstalk between these debilitating events is poorly understood. The present study was aimed to reveal the mechanism behind α-syn-induced glial inflammation and α-syn spreading in brains of α-synucleinopathy and to find out therapeutic interventions against α-syn pathology.
Methods:
α-Syn preformed fibrils (PFF) were prepared *in vitro* and validated by electron microscope. Induction of inflammation in microglia by PFF was measured by real time PCR. TLR2 and NF-kB activation were assessed by immunoprecipitation and EMSA respectively. A peptide corresponding to the TLR2-interacting domain of MyD88 (TIDM) was designed and its efficacy on TLR2 inhibition was measured in primary microglia and in A53T animal brains. α-Syn propagation *in vivo* was evaluated in PFF-seeded A53T mice brains by immunostaining of α-syn in different brain regions. Parkinsonian pathologies in mice were monitored by counting nigral dopaminergic neurons, measuring striatal dopamine level and by conducting behavioral assays. Statistical analyses were performed by unpaired t test and by one way or two way ANOVA depending on the experiments. GraphPad Prism v7.02 was used for statistical analyses.
Results:
The data demonstrated that PFF increased the association between TLR2 and MyD88 to cause microglial activation and that selective inhibition of TLR2 activation by TIDM peptide reduced PFF-induced microglial inflammation without altering phagocytosis. Accordingly, either nasal administration of TIDM peptide or genetic deletion of TLR2 reduced glial inflammation, decreased α-syn spreading and protected dopaminergic neurons in PFF-seeded A53T mice. At the molecular level, we observed that microglia-derived proinflammatory molecules increased the transcription of α-syn gene in neurons via activation of NF-κB and that selective inhibition of NF-κB by nasal wild type NEMO-binding domain (wtNBD) peptide also decreased α-syn spreading and protected dopaminergic neurons.
Conclusion:
It can be surmised from the findings that α-syn spreading majorly depends on the TLR2/MyD88/NF-κB pathway and targeting this pathway by TIDM or NBD peptides might have significant therapeutic potential against α-syn pathology.