Absence of TLR4 reduces neuroinflammation in an experimental in vivo model of Parkinson's disease.

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Parkinson`s disease (PD) is a progressive, disabling neurodegenerative disorder. PD is characterized by the degeneration of dopaminergic nigrostriatal neurons, which results in disabling motor disturbances. Drugs currently used to treat neurological disease and injuries, provide temporary relief of symptoms but they don’t stop or slow the underlying neurodegenerative process. Recent studies demonstrated the expression of TLR4 in different anatomical areas of the central nervous system (CNS), and in particular demonstrated that TLR4-deficient mice were greater protected when stimulated with MPTP-induce PD and this is correlates with decreased microglial activation in the SN, suggesting that dopaminergic cell death is TLR4-dependent.

In the present study we wanted to demonstrate, using an in vivo model of Parkinson's disease, how the TLR4 plays an important role in the pathogenesis of Parkinson's disease. Here we usied 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine (MPTP) model because it produces clinical, biochemical and neuropathological changes similar to those observed in human PD. Our experiments have shown that in C57/BL6 WT mice, the administration of MPTP (20 mg/Kg, ip) causes an increase of proteins levels involved in the pathway of TLR4, such as MyD88 and TRAF6. The expression of these proteins, decreases visibly in TLR4 KO mice subject to administration of MPTP. Furthermore, the absence of TLR4 also has an important impact on inflammatory and apoptotic processes. In fact, by western blot analysis was demonstrated the different expression of IκB-α, NFκB p65, iNOS and COX-2 in mice WT and TLR4 KO following the administration of MPTP. Also the activation of astrocytes was lower in mesencephalon from TLR4 KO mice. Moreover, in our study, we demonstrated that in WT mice there is a greater depressed mood than TLR4 KO mice.

Our results clearly demonstrated that absence of TLR4 reduces the development of neuroinflammation associated with PD. Therefore, TLR4 could be considered as a possible therapeutic target in a neurodegenerative disorders like PD.