Inducible TLR4 Decoy for Targeting Microglial Activation to Reduce Neuronal Degeneration in Parkinson's Disease

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Parkinson's disease progression is worsened by chronic neuroinflammation and excessive microglial activation, making inflammatory pathways promising therapeutic targets. Among these strategies, gene therapy is especially attractive because it can provide localized, sustained treatment, although constitutive expression carries clinical risk. To test this in vitro, I designed an inducible decoy receptor for Toll-like receptor 4 (TLR4), a major player in neuroinflammation. The decoy consists of a truncated TLR4 extracellular domain fused to the human Fc region, to sequester pro-inflammatory ligands without activating downstream TLR4 signaling. Using a doxycycline-dependent Tet-On 3G system, the decoy's efficacy was evaluated in BV2 (microglial cell line) with rotenone, an inducer of activation-induced cell death in BV2. TLR4 decoy treatment significantly improved BV2 survival and prevented the transition to an amoeboid morphology after rotenone activation. To test whether suppressing BV2 activation confers neuroprotection, differentiated MN9D (dopaminergic neuronal cell) were co-cultured with activated BV2 cells. Adding the TLR4 decoy to the co-culture significantly increased MN9D viability. Next, the inducible TLR4 decoy was delivered into MitoPark mice, a model of Parkinson's disease. This treatment improved locomotion and reduced microglial over-activation in 20-week-old MitoPark mice, suggesting that sequestering TLR4-mediated inflammatory signaling is a plausible strategy for mitigating neurodegeneration in PD. Together, these findings support inducible anti-inflammatory gene therapy targeting TLR4 as a promising strategy to protect dopaminergic neurons and slow neurodegeneration in PD.

Awards Won:
Fourth Award of $600